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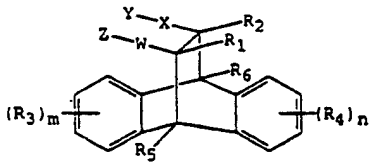

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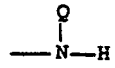

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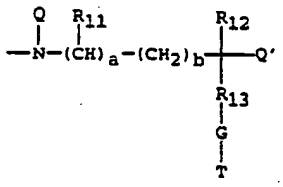

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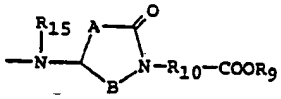

(iv)

(57) Abstract

Compounds of formula (I) wherein W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group or -C(O)-CH_2- (in which the carbonyl group is bonded to Y), provided that at least one of W and X contains carbonyl, Y is R_7-O- or R_7-N(R_8)- (wherein R_7 is H or C_1 to C_{15} hydrocarbyl, up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom provided that Y does not contain a -O-O- group, and R_8 is H, C_1 to C_3 alkyl, carboxymethyl or esterified carboxymethyl), Z is selected from (i) -O-R_9, (ii), (iii), (iv), wherein R_9-R_{13}, Q, Q', G, T, A, B, a and b are as defined in claim 1; or Z is absent and W is H, R_1 is H, methyl, halo, carboxy, esterified carboxy, amidated carboxy, carboxymethyl, esterified carboxymethyl or amidated carboxymethyl, R_2 is selected from the groups recited above for R_1; R_3 and R_4 (or each R_3 and R_4 group, when m or n is 2 or more) are independently selected from halo, amino, nitro, cyano, sulphamoyl, C_1 to C_3 alkyl, C_1 to C_3 alkoxy, carboxy, esterified carboxy and amidated carboxy, R_5 and R_6 are independently selected from H and the groups recited above for R_3; m, n = 0 to 4, with provisos as given in claim 1 and pharmaceutically acceptable salts thereof, are ligands at cholecystokinin and/or gastrin receptors.

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BICYCLO[2.2.2] OCTANE DERIVATIVES AS CHOLESTOCYSTOKININ INHIBITORS

This invention relates to bicyclo[2.2.2]octane derivatives, and more particularly to bicyclo[2.2.2]octane derivatives which bind to cholecystokinin and/or gastrin receptors. The invention also relates to methods for preparing such bicyclo[2.2.2]octane derivatives and to compounds which are useful as intermediates in such methods.

Gastrin and the CCK's are structurally-related neuropeptides which exist in gastrointestinal tissue and in the CNS (see Mutt V., Gastrointestinal Hormones, Glass G.B.J., ed., Raven Press, N.Y., p 169 and Nisson G., ibid, p. 127).

Gastrin is one of the three primary stimulants of gastric acid secretion. Several forms of gastrin are found including 34-, 17-, and 14-amino acid species with the minimum active fragment being the C-terminal tetrapeptide (TrpMetAspPhe-NH_2) which is reported in the literature to have full pharmacological activity (see Tracey H.J. and Gregory R.A., Nature (London), 1964, 204, 935). Much effort has been devoted to the synthesis of analogues of this tetrapeptide (and the N-protected derivative Boc-TrpMetAspPhe-NH_2) in an attempt to elucidate the relationship between structure and activity.

Natural cholecystokinin is a 33 amino acid peptide (CCK-33), the C-terminal 5 amino acids of which are identical to those of gastrin. Also found naturally is the C-terminal octapeptide (CCK-8) of CCK-33.

The cholecystokinins are reported to be important in the regulation of appetite. They stimulate intestinal motility, gall bladder contraction, pancreatic enzyme secretion, and are known to have a trophic action on the pancreas. They also inhibit gastric emptying and have various effects in the CNS.

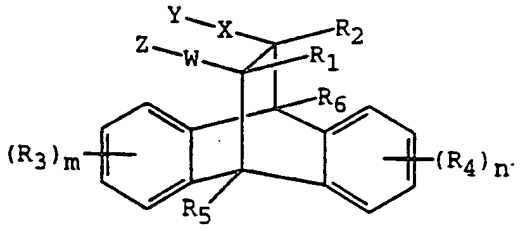
Compounds which bind to cholecystokinin and/or gastrin receptors are important because of their potential pharmaceutical use as

antagonists of the natural peptides.

A number of gastrin antagonists have been proposed for various therapeutic applications, including the prevention of gastrin-related disorders, gastrointestinal ulcers, Zollinger-Ellison syndrome, antral G Cell hyperplasia and other conditions in which lowered gastrin activity is desirable. The hormone has also been shown to have a trophic action on cells in the stomach and so an antagonist may be expected to be useful in the treatment of cancers, particularly in the stomach.

Possible therapeutic uses for cholecystokinin antagonists include the control of appetite disorders such as anorexia nervosa, and the treatment of pancreatic inflammation, biliary tract disease and various psychiatric disorders. Other possible uses are in the potentiation of opiate (e.g. morphine) analgesia, and in the treatment of cancers, especially of the pancreas. Moreover, ligands for cholecystokinin receptors in the brain (so-called CCK_B receptors) have been claimed to possess anxiolytic activity.

According to the present invention, there are provided compounds for use in therapy (and particularly for use as gastrin and/or CCK antagonists), such compounds being of the formula



wherein

W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group or $-C(O)-CH_2-$ (in which the carbonyl group is bonded to Y), provided that at least one of W and X contains carbonyl,

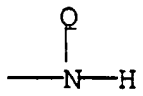
Y is R_7-O- or $R_7-N(R_8)-$ (wherein R_8 is H or C_1 to C_{15} hydrocarbyl, up to two carbon atoms of the hydrocarbyl

moiety optionally being replaced by a nitrogen, oxygen or sulphur atom provided that Y does not contain a -O-O- group, and R_8 is H, C_1 to C_3 alkyl, carboxymethyl or esterified carboxymethyl),

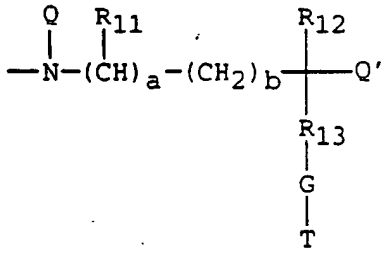
Z is selected from

i) $-O-R_9$

wherein R_9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

ii) 

wherein Q is H, C_1 to C_5 hydrocarbyl, or $-R_{10}-U$, wherein R_{10} is a bond or C_1 to C_3 alkylene and U is aryl, substituted aryl, heterocyclic, or substituted heterocyclic,

iii) 

wherein a is 0 or 1 and b is from 0 to 3,

R_{11} is H or methyl,

R_{12} is H or methyl; or R_{12} is $CH_2=$ and Q' is absent; or R_{11} and R_{12} are linked to form a 3- to 7-membered ring,

R_{13} is a bond or C_1 to C_6 hydrocarbylene,

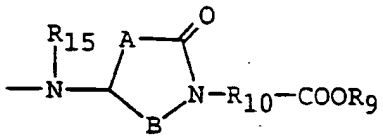
G is a bond, -CHOH- or -C(O)-

Q' is as recited above for Q or

$-R_{10}-(C(O))_d-L-(C(O))_e-R_9$ (wherein R_9 and R_{10} are as defined above, L is O, S or $-N(R_{14})-$, in which R_{14} is as defined above for R_8, and d and e are 0 or 1, provided that d+e<2); or Q' and R_{12}, together with the carbon atom to which they are attached, form a 3- to 7-membered ring,

Q is as defined above; or Q and R_{12} together form a group of the formula $-(CH_2)_f-V-(CH_2)_g-$ wherein V is -S-, -S(O)-, $-S(O)_2-$, $-CH_2-$, -CHOH- or -C(O)-, f is from 0 to 2 and g is from 0 to 3; or, when Q' is $-R_{10}-U$ and U is an aromatic group, Q may additionally represent a methylene link to U, which link is *ortho* to the R_{10} link to U,

T is H, cyano, C_1 to C_4 alkyl, $-CH_2OH$, carboxy, esterified carboxy or amidated carboxy; or

iv) 

wherein A and B are independently a bond or C_1 to C_3 alkylene, provided that A and B together provide from 2 to 4 carbon atoms in the ring, R_9 and R_{10} are as defined above, and R_{15} is as defined above for R_8

or Z is absent and W is H,

R_1 is H, methyl, halo, carboxy, esterified carboxy, amidated carboxy, carboxymethyl, esterified carboxymethyl or amidated carboxymethyl,

R_2 is selected from the groups recited above for R_1; or, when Z is absent and W is H, R_2 may additionally

represent -C(O)-Z' wherein Z' is selected from the groups recited above for Z; or R_1 and R_2 together form a second bond between the carbon atoms to which they are attached,

R_3 and R_4 (or each R_3 and R_4 group, when m or n is 2 or more) are independently selected from halo, amino, nitro, cyano, sulphamoyl, C_1 to C_3 alkyl, C_1 to C_3 alkoxy, carboxy, esterified carboxy and amidated carboxy

R_5 and R_6 are independently selected from H and the groups recited above for R_3

m is from 0 to 4, provided that m is not more than 2 unless R_3 is exclusively halo,

n is from 0 to 4, provided that n is not more than 2 unless R_4 is exclusively halo,

or pharmaceutically acceptable salts thereof.

Compounds according to the above definition are believed to be novel *per se*, provided that

if one (but only one) of R_1 and R_2 is methyl, m and n are not both 0,

Z is not methoxy when Y is methoxy,

Z and Y are not *trans* to each other when Z is R_8-O- and Y is R_7-O- , and

if Z is absent and R_1 and R_2 are both H, Y is not R_7-O-.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as

alkylaryl, alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups,

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as methyl adamantyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above.

A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring. Examples include thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine. Most usually, however, halogen substituents in the compounds of the invention are chlorine or fluorine substituents.

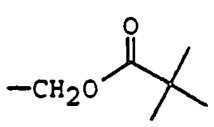
Preferably, m and n are both 0. However, when m and n are not both 0, R_3 and R_4 are preferably selected from halo, amino, nitro, cyano, sulphamoyl, C_1 to C_3 alkyl and C_1 to C_2 alkoxy. As mentioned above, when m or n is 2 or more, each R_3 and R_4 group is independent of the others. For example, the compounds of the

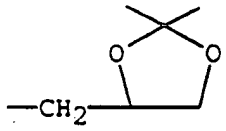
invention may include two different R_3 groups.

Particularly preferred groups for R_5 and R_6 are hydrogen and the groups just recited for R_3, and especially hydrogen, methyl and fluoro.

When reference is made herein to a "substituted" aromatic group, the substituents will generally be from 1 to 3 in number (and more usually 1 or 2 in number), and selected from the groups recited above for R_3.

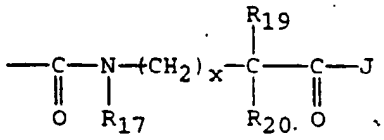
An "esterified" carboxy group, as the term is used herein, is preferably of the form $-COOR_{16}$, wherein R_{16} is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:





Most commonly, R_{16} is C_1 to C_5 alkyl, benzyl or substituted benzyl, and particularly C_1 to C_5 alkyl. Similarly, an "amidated" carboxy group is preferably of the form $-CONR_{17}R_{18}$ wherein R_{17} and R_{18} are independently H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl.

In the case of the group T, preferred amidated carboxy groups take the form $-CONR_{17}R_{18}$ (wherein R_{17} and R_{18} are as defined above) or

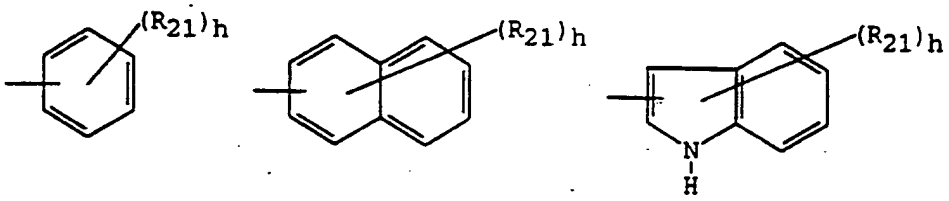


wherein R_{17} is as defined above, R_{19} and R_{20} are independently H or methyl, or R_{19} and R_{20} (together with the carbon atom to which they are attached) form a 3- to 7-membered carbocyclic group, J is -OH,

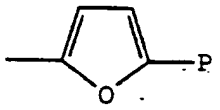
$-O-R_{16}$ or $-NHR_{18}$, wherein R_{16} and R_{18} are as defined above, and x is 0 to 3.

When R_{11} and R_{12} are linked to form a ring, such ring will generally be saturated, and usually also carbocyclic. Similarly, when Q' and R_{12} are linked to form a ring, this will also usually be saturated and carbocyclic.

Exemplary carbocyclic and heterocyclic groups which may form the group U include:

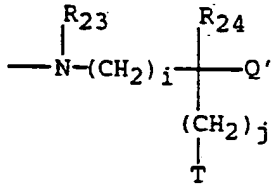


wherein R_{21} is as defined above for R_5, and h is from 0 to 3, and



wherein P is H or $-COOR_{22}$, in which R_{22} is as defined above for R_{17}.

Z is preferably $-NH_2$, $-O-R_9$ or



wherein i is from 0 to 4, j is from 0 to 3, R_{23} and R_{24} are independently H or methyl, or R_{23} and R_{24} together form a group of the formula $-(CH_2)_k-V'-CH_2-$ (wherein V' is $-CH_2-$, -CHOH- or -C(O)-, and k is 0 to 2). Most commonly, i is 0 or 1 and j is 0 to 2.

When W is sulphinyl, Y is preferably R_7-NH-.

Preferably, R_7 is C_6 to C_8 straight or branched chain alkyl, or $R_{25}-(CH_2)_p-$, wherein R_{25} is selected from phenyl, 1-naphthyl, 2-

naphthyl, indolyl, norbornyl, adamantyl or cyclohexyl, and p is from 0 to 3.

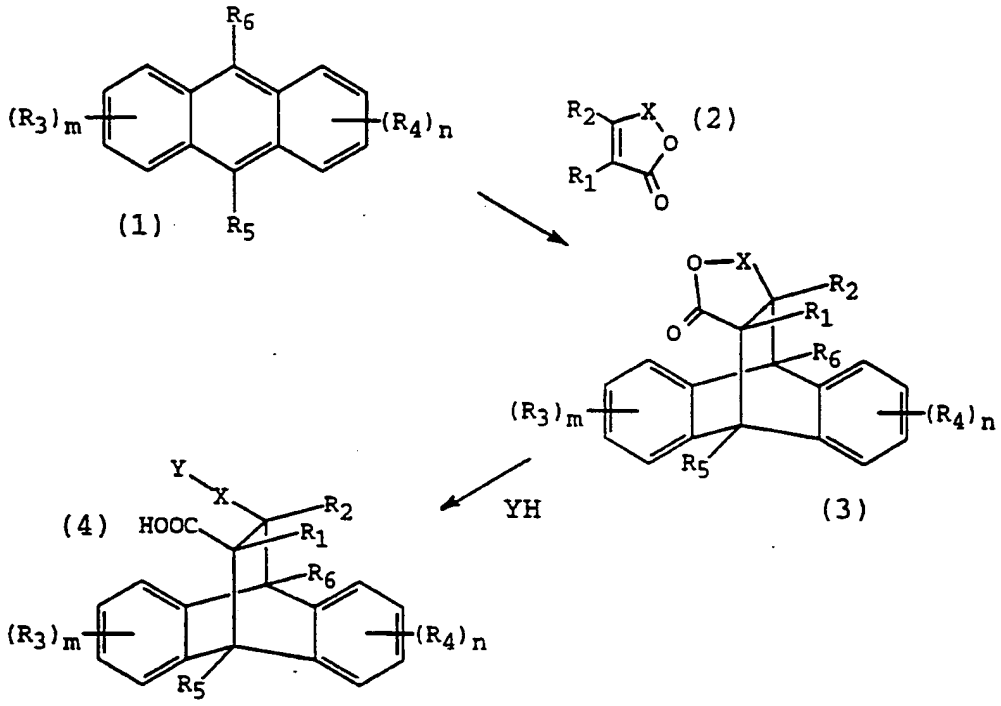
Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with alkali metals and alkaline earth metals, such as sodium, potassium, calcium and magnesium, and salts with organic bases. Suitable organic bases include amines such as N-methyl-D-glucamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable acids include hydrochloric acid, phosphoric acid, oxalic acid, maleic acid, succinic acid and citric acid.

The compounds of the invention exist in various enantiomeric and diastereomeric forms as a result of the asymmetric carbon atoms to which W and X are attached. It will be understood that the invention comprehends the different enantiomers and diastereomers in isolation from each other, as well as mixtures of enantiomers and diastereomers. Also, the structural formulae herein show the groups W and X arranged *cis* to each other, but it will be appreciated that the invention includes the corresponding *trans* isomers.

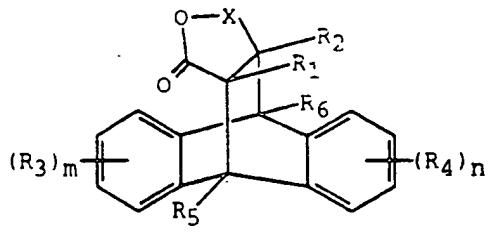
Compounds according to the present invention in which W is a carbonyl group, X is carbonyl or sulphonyl, and Z is OH may conveniently be made by the process depicted in Reaction Scheme A.

Reaction Scheme A



In this scheme, anthracene or an anthracene derivative (1) is reacted with the acid anhydride (2) in a Diels-Alder reaction. The reactants are conveniently refluxed together in a suitable solvent such as toluene to form the adduct (3). In some cases, it may be appropriate to conduct the reaction at elevated pressure and/or in the presence of a Lewis acid catalyst. The adduct (3) is then reacted with a compound of the formula YH (ie. either an alcohol or an amine) to form the acid compound (4). If YH is an amine, the reaction is suitably carried out in a solvent such as THF in the presence of a catalytic amount of DMAP. If YH is an alcohol, the reaction may be conducted in pyridine at elevated temperature.

The invention therefore also provides a method of making compounds wherein W is carbonyl and X is carbonyl or sulphonyl, said method including the step of reacting a compound of the formula



with a compound of formula YH.

The equivalent *trans* adducts can be prepared using a suitably differentiated fumaric acid (eg the mono methyl mono benzyl diester), which, after addition to anthracene or an anthracene derivative (1), allows independent elaboration of the two sidechains.

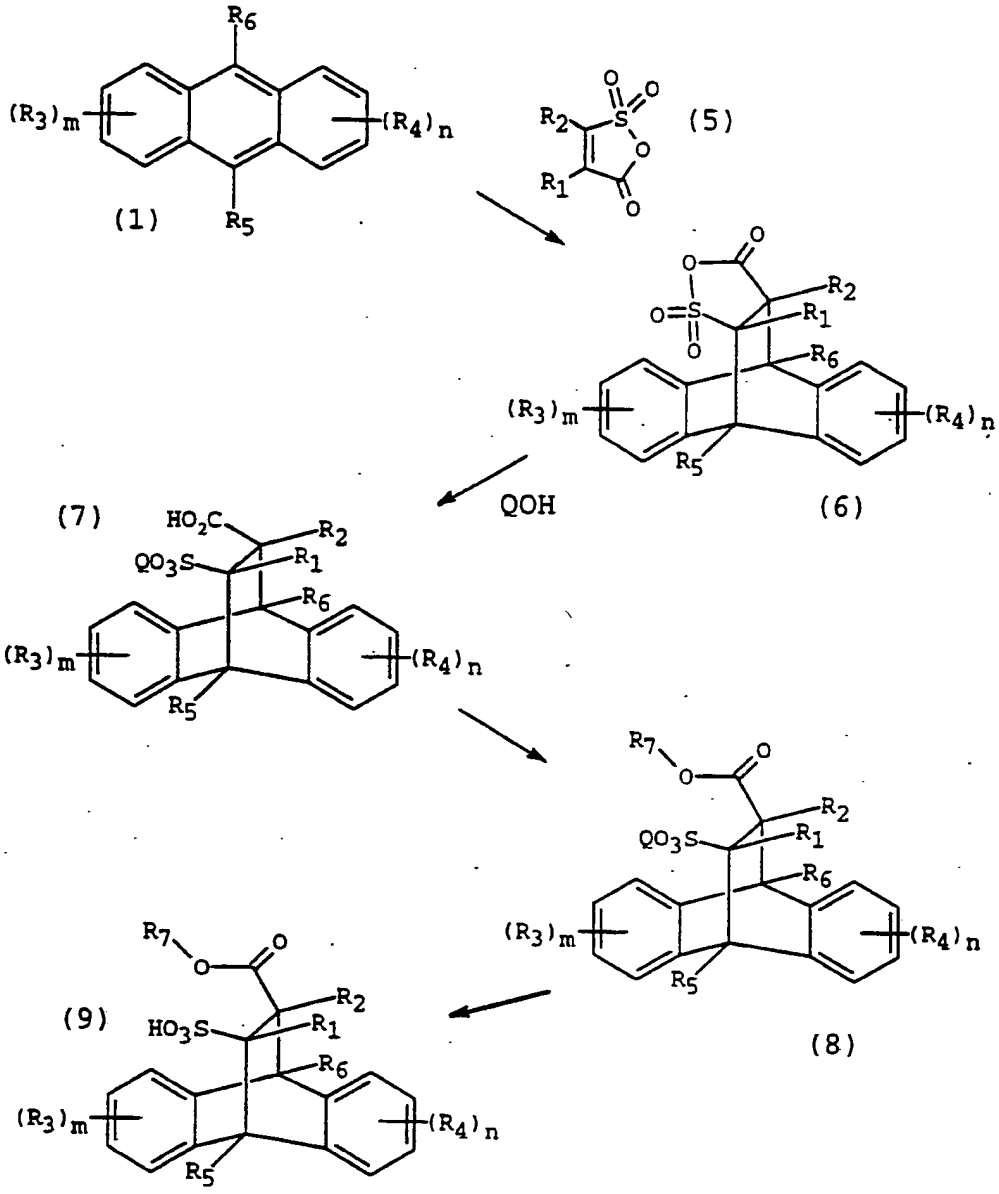
Compounds in which Z is other than OH may of course be made from the acid compound (4) by conventional esterification or amidation reactions. Suitable amidation methods are described in detail in "The Peptides, Vol. 1", Gross and Meinenhofer, Eds., Academic Press, N.Y., 1979. These include the carbodiimide method (using, for example, 1,3-dicyclohexylcarbodiimide [DCC] or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride [EDCI], and optionally an additive such as 1-hydroxybenzotriazole [HOBT] to prevent racemization), the azide method, the mixed anhydride method, the symmetrical anhydride method, the acid chloride method, the use of bis (2-oxo-3-oxazolidinyl) phosphinic chloride [BOP-Cl], the use of PyBOP, the use of the isopropenylsuccinimido carbonate method and the active ester method (using, for example, N-hydroxysuccinimide esters, 4-nitrophenyl esters or 2,4,5-trichlorophenol esters).

The coupling reactions are generally conducted under an inert atmosphere, such as an atmosphere of nitrogen or argon. Suitable solvents for the reactants include methylene chloride, tetrahydrofuran [THF], dimethoxyethane [DME] and dimethylformamide [DMF].

A procedure analogous to that shown in reaction scheme A may also

be used as the basis for preparing the compounds of the invention in which W is sulphonyl and Y is R_7-O-, as depicted in reaction scheme B below:

Reaction Scheme B

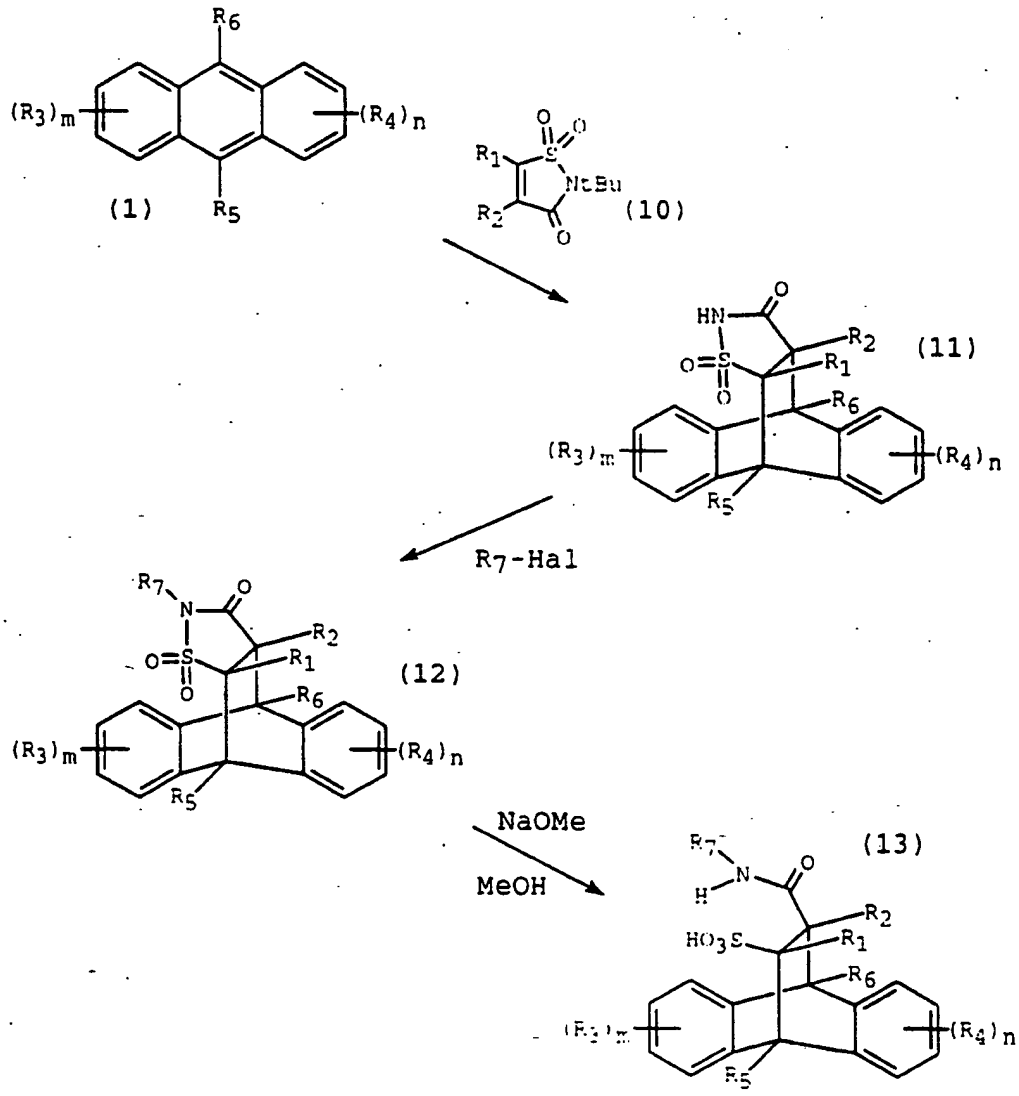


In this case, the Diels-Alder adduct (6) is opened with an alcohol such as benzyl alcohol (represented as QOH), so that product (7) is the corresponding sulphonyl ester. The free carboxylic acid group of this sulphonyl ester may then be esterified by conventional methods, followed by hydrogenolysis of the product (8)

to yield the desired sulphonic acid carboxylic ester (9).

The compounds of the invention in which W is sulphonyl and Y is R_7-NH- may be prepared by analogous means, in which compound (7) is amidated (rather than esterified) prior to hydrogenolysis. Alternatively, a process such as is depicted in reaction scheme C may be employed:

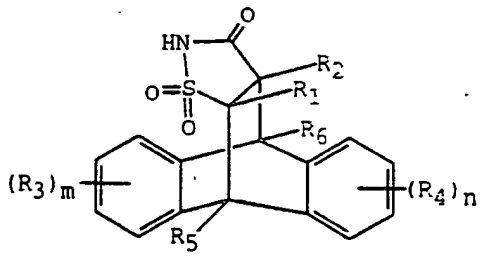
Reaction Scheme C



In this scheme, anthracene or an anthracene derivative (1) is reacted with the N-protected compound (10) in a Diels-Alder reaction analogous to that of the first step in reaction scheme A.

The deprotected product Diels-Alder adduct (11) is then reacted with a compound of the formula R_7-Hal (wherein Hal represents a halogen atom) to form compound (12). The N-containing ring may then be opened using an alkoxide (eg. sodium methoxide in methanol) to produce the target compound (13).

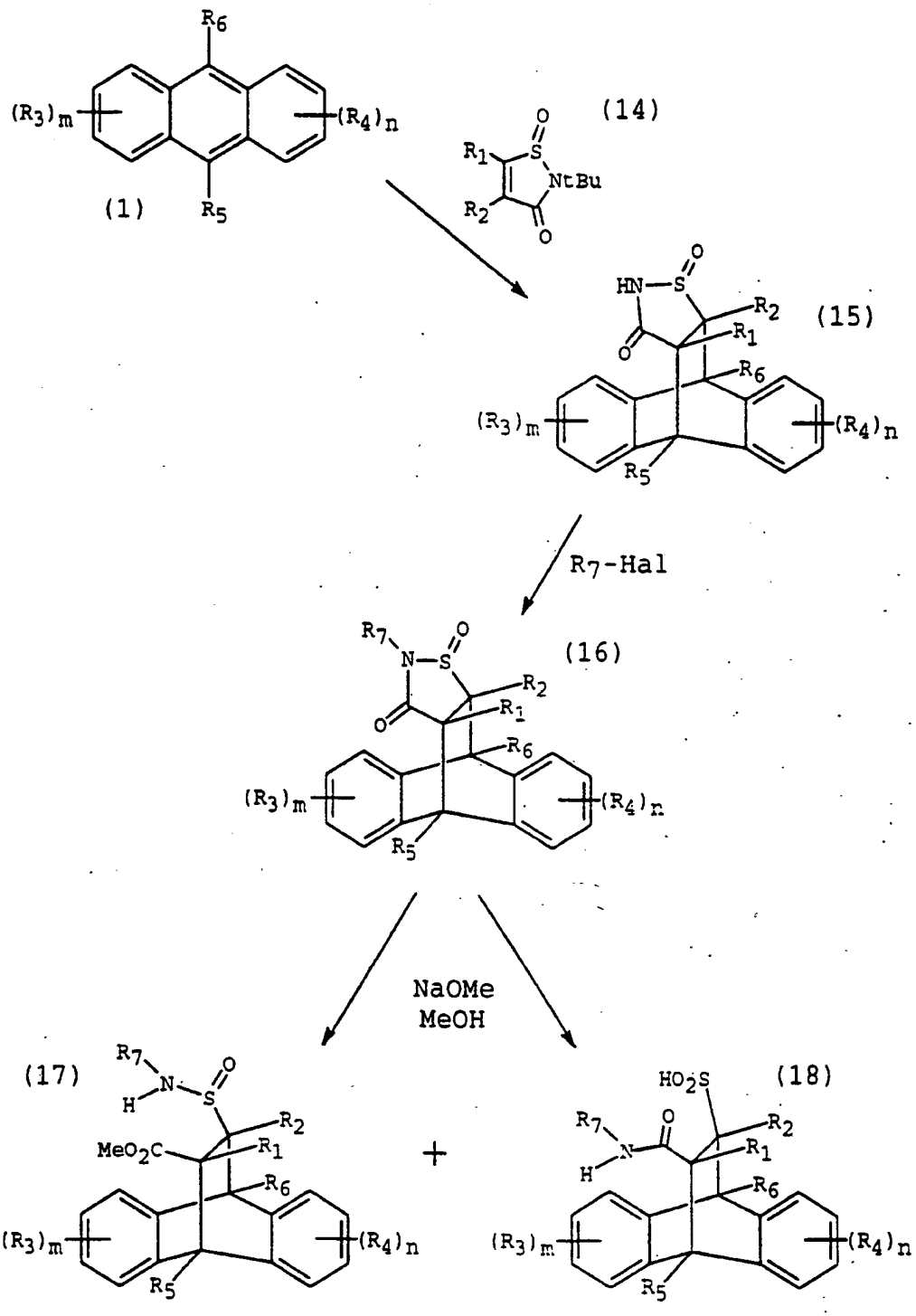
The invention therefore also provides a method of making compounds wherein W is sulphonyl and Y is R_7-NH-, said method comprising the step of reacting a compound of the formula



with a compound of the formula R_7-Hal, and then reacting the product with an alkoxide.

Compounds of the invention wherein W or X is a sulphinyl group may conveniently be prepared by the route shown in reaction scheme D:

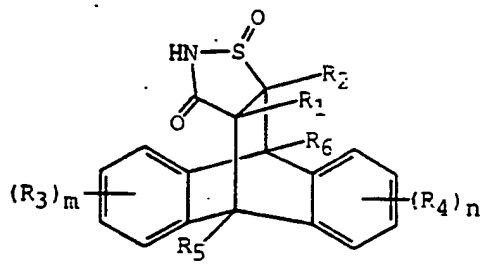
Reaction Scheme D



Reaction scheme D is analogous to reaction scheme C, except that the sulphinyl analogue of compound (10) is used in the Diels-Alder

reaction, to yield the sulphinyl analogue of adduct (12). This can then be opened both ways to give on the one hand the sulphinamide acid alkyl ester (17), and on the other the sulphinic acid amide (18). The free sulphinamide acid can of course be obtained from the alkyl ester (12) by conventional methods.

Accordingly, the invention also provides a method of making compounds wherein W or X is sulphinyl, said method comprising the step of reacting a compound of the formula:



with a compound of the formula R_7-Hal, and then reacting the product with an alkoxide.

While reaction schemes C and D above lead to the free sulphonic or sulphinic acid compounds, it will be appreciated that the corresponding ester or amide derivatives can be prepared from the free acid compounds by conventional methods. Most usually, coupling of the sulphonic or sulphinic acid compounds will be *via* the corresponding sulphonic or sulphinic acid chlorides.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

The compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an

aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

The invention is now further illustrated by means of the following examples.

Example 1 Preparation of (±)-cis-8-(3-phenylpropylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

a. 2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid

anhydride

Anthracene (8.9 g, 0.05 mol) and maleic anhydride (4.9 g, 0.05 mol) were refluxed for 3h in toluene (200 ml). Upon cooling, the title compound was obtained as white crystals which were isolated by filtration (10.2g 74%).

b. (±)-cis-8-(3-phenylpropylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride (107 mg, 0.39 mmol) and 1-phenyl-3-propylamine (55 mg, 0.4 mmol) were dissolved in dry THF (5 ml) and DMAP (2 mg) was introduced. The mixture was stirred at room temperature overnight during which time a thick white precipitate formed. The solid was filtered off, washed with THF and dried to give the title compound (100 mg 62%), mp 190-1°, found: C, 78.82; H, 5.99; N, 3.40. $C_{27}H_{25}NO_3$ requires C, 78.81; H, 6.12; N, 3.38%

Example 2 Preparation of (±)-cis-8-(2-(3-indolyl)ethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that tryptamine was used instead of 1-phenyl-3-propylamine in step b. Yield 84%, m.p. 137-8°, found: C, 74.13; H, 6.12; N, 5.73. $C_{28}H_{24}N_2O_3$. 0.7 H_2O. 0.6 THF requires C, 74.16; H, 6.18; N, 5.69%

Example 3 Preparation of (±)-cis-8-(phenylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that benzylamine was used instead of 1-phenyl-3-propylamine in step b. Yield 27%, m.p. 194-5°, found: C, 77.35; H, 5.97; N, 3.36. $C_{25}H_{21}NO_3$. 0.5 THF requires C, 77.30; H, 6.18; N, 3.34%

Example 4 Preparation of (±)-cis-8-(1-naphthylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that 1-naphthylmethylamine was used instead of 1-phenyl-3-propylamine in step b. Yield 35%, m.p. 135-7°, found: C, 78.37; H, 6.07; N, 2.98. $C_{29}H_{23}NO_3$. 1.0 THF requires C, 78.39; H, 6.18; N, 2.77%

Example 5 Preparation of (±)-cis-8-(2-naphthylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that 2-naphthylmethylamine was used instead of 1-phenyl-3-propylamine in step b. Yield 35%, m.p. 247-8°, found: C, 80.46; H, 5.03; N, 3.32. $C_{29}H_{23}NO_3$ requires C, 80.46; H, 5.03; N, 3.23%

Example 6 Preparation of (±)-cis-8-(2-norbornylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that 2-norbornylmethylamine was used instead of 1-phenyl-3-propylamine in step b. Yield 24%, m.p. 127-9°, found: C, 74.93; H, 7.07; N, 3.76. $C_{26}H_{27}NO_3$. 0.75 H_2O requires C, 75.24; H, 6.92; N, 3.38%

Example 7 Preparation of (±)-cis-8-(hexylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 except that hexylamine (2eq) was used instead of 1-phenyl-3-propylamine in step b. and the product was precipitated with 2M HCl and then filtered and washed with water. Yield 91%, m.p. 174-6°, found: C, 76.52; H, 7.24; N, 3.98. $C_{24}H_{27}NO_3$ requires C, 76.36; H, 7.21; N, 3.71%

Example 8 Preparation of (±)-cis-8-(octylaminocarbonyl)-

2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 7 except that octylamine was used instead of hexylamine. Yield 89%, m.p. 116-8°, found: C, 76.83; H, 7.70; N, 3.58. $C_{2t}H_{31}NO_3$ requires C, 77.01; H, 7.71; N, 3.45%

Example 9 Preparation of (±)-cis-8-(cyclohexylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 7 except that cyclohexylmethylamine was used instead of hexylamine. Yield 93%, m.p. 185-7°, found: C, 76.88; H, 7.09; N, 3.69. $C_{25}H_{27}NO_3$ requires C, 77.09; H, 6.99; N, 3.60%

Example 10 Preparation of (±)-cis-8-(3,3-dimethylbutylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 7 except that 3,3-dimethylbutylamine was used instead of hexylamine. Yield 25%, m.p. 128-30°, found: C, 75.56; H, 7.22; N, 3.92. $C_{24}H_{27}NO_3.0.2\ H_2O$ requires C, 75.64; H, 7.25; N, 3.68%

Example 11 Preparation of (±)-cis-8-(1-adamantylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride (prepared in example 1 step a) (276 mg, 1.0 mmol) was dissolved in THF (5 ml) and 1-adamantamine (215 mg, 1.4 mmole) was added followed by triethylamine (0.16 ml). The solution was heated at a gentle reflux for 1.5 h and the clear solution on cooling was poured onto 2M HCl (20 ml). The resulting gummy solid was extracted with dichloromethane (10 ml) and the organic layer was dried, filtered and evaporated. The residue was taken up in methanol (5 ml) and diluted with water (5 ml) to precipitate a white solid.

This was filtered off and dried. The product (230 mg, 54%), m.p. 234-5°, found: C, 76.14; H, 6.72; N, 3.10. $C_{28}H_{29}NO_3.0.75\ H_2O$ requires C, 76.25; H, 6.97; N, 3.17%

Example 12 Preparation of (±)-cis-8-(2-(1-adamantyl)ethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 11 except that 1-adamantylethylamine was used instead of 1-adamantylamine. Yield 26%, m.p. 138-40°, found: C, 77.31; H, 7.21; N, 2.70. $C_{30}H_{33}NO_3.0.6\ H_2O$ requires C, 77.26; H, 7.39; N, 3.00%

Example 13 Preparation of (±)-cis-8-(-1-adamantylmethyloxy-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride (prepared in example 1 step a) (276 mg, 1.0 mmol) and 1-adamantanemethanol (166 mg, 1.0 mmol) were heated together in pyridine (2 ml) at 100° for 4 h. After cooling the solution was poured onto 2M HCl and extracted with dichloromethane (20 ml). The solution was dried filtered and evaporated to leave a white residue which was further purified by column chromatography (silica dichloromethane\ethyl acetate\methanol 9:1:0.5 as eluent). The product was further triturated with hexane to leave the title compound (110 mg, 25%), m.p. 165°, found: C, 77.14; H, 6.88. $C_{29}H_{30}O_4.0.5\ H_2O$ requires C, 77.13; H, 6.91%

Example 14 Preparation of (±)-cis-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride (prepared in example 1 step a) (276 mg, 1.0 mmol) and 1-adamantanemethylamine (182 mg, 1.1 mmol) were dissolved in dry THF (5 ml) and refluxed for 1h. A thick white precipitate was formed and this was isolated by filtration and washed with THF to

leave the title compound (320 mg, 72%), m.p. 237-9°, found: C,78.76; H, 7.18; N, 3.33. $C_{29}H_{31}NO_3$ requires C, 78.88; H, 7.08; N, 3.17% The compound was further characterised as the N-methyl-D-glucamine salt found: C, 63.48; H, 7.61; N, 3.79. $C_{36}H_{48}N_2O_8 . 2.5H_2O$ requires C, 63.42; H, 7.83; N, 4.11%

Example 15 Preparation of (±)-cis-7-(methoxycarbonylmethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane.

(±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7-carboxylic acid prepared as in example 14 (441 mg, 1.0 mmol) was dissolved in warm DMF (5 ml) and then the solution was cooled to 0°. N-hydroxysuccinimide (115 mg, 1.0 mmol) was added followed by DCCI (206 mg, 1.0 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The white precipitate was removed by filtration. Triethylamine (0.2 ml) was added to the filtrate followed by glycine methyl ester hydrochloride (125 mg, 1 mmol) and the reaction mixture was stirred for a further 24h. The reaction mixture was poured onto a mixture of 2M HCl and ice. The white precipitate was isolated by filtration and washed well with water and dried. The solid was taken up in ethyl acetate (20 ml) and filtered through celite. The residue on evaporation was triturated with methanol leaving a white crystalline solid (125 mg, 24%), m.p. 209-11°, found: C,74.16; H, 7.14; N, 5.53 $C_{32}H_{36}N_2O_4$ requires C, 74.19; H, 7.12; N, 5.40%

Example 16 Preparation of (±)-cis-7-(carboxymethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

a. (±)-cis-7-(benzyloxycarbonylmethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane

(±)-Cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid (prepared as in example 14)

(440 mg, 1 mmole) and PyBOP (520 mg, 1 mmole) were taken up in dry dichloromethane (15 ml) and Hunigs base (0.52 ml, 3 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. glycine benzyl ester 4-toluenesulphonic acid salt (340 mg, 1 mmole) was added and the mixture stirred overnight. The organic layer was washed with 5% potassium hydrogensulphate (15 ml), sodium hydrogencarbonate (15 ml) and saturated brine (15 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography on silica using 80% ethyl acetate and 20% hexane as eluent. The title compound (510 mg, 87%) was isolated as a white solid, m.p. 130-3°

b. (±)-cis-7-(carboxymethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The product of step a (350 mg, 0.59 mmole) was dissolved in methanol (20 ml) and 10% palladium on charcoal (100 mg) was added. The mixture was stirred under an atmosphere of hydrogen for 3h. The product was filtered through celite and on evaporation yielded the title compound (0.30 g, 100%). The product was characterised and tested as the N-methyl-D-glucamine salt, m.p. 110-2°, found: C, 63.42; H, 7.55; N, 5.66. $C_{38}H_{51}N_3O_6$. 1.5 H_2O requires C, 63.42; H, 7.68; N, 5.66%.

Example 17 Preparation of methyl (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylate

2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride (prepared as in example 1 step a) (2.76 g, 6.0 mmol), methanol (0.41 ml) and DMAP (20 mg) were stirred in pyridine (5 ml). The solution was stirred and refluxed for 4h, poured onto 2M HCl (50 ml) and extracted with dichloromethane. The organic layer was washed with mor 2M HCl and then water. The solution was dried filtered and evaporated to yield the crude monoester (1.7 g). This material (308 mg, 1mmol) and 1-adamantanemethylamine (181 mg, 1.0 mmol) were dissolved in dry dichloromethane (10 ml) and diisopropylethylamine (0.35 ml) was added followed by PyBOP (520

mg, 1 mmol). The solution was stirred at room temperature for 72h. It was then evaporated and the residue taken up in ethyl acetate and washed successively with 5% aqueous potassium hydrogensulphate (3x40 ml), saturated aqueous sodium hydrogencarbonate (40 ml) and brine (40 ml). The organic layer was dried, filtered and evaporated to leave a foam that was purified by column chromatography (silica eluent 90% dichloromethane and 10% ethyl acetate). Further purification was achieved by recrystallisation from methanol. Yield 200 mg, 44%, m.p. 227-30°, found: C,79.06; H, 7.54; N, 2.94. $C_{30}H_{33}NO_3$ requires C, 79.09; H, 7.30; N, 3.07%

Example 18 Preparation of (±)-cis-8-(2-naphthylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-sulphonic acid

a. Diels-Alder adduct of anthracene and 3-oxo-2,3-dihydro-isothiazolone

N-t-butyl-3-oxo-2,3-dihydroisothiazolone (prepared as in Helv.Chim. Acta., 1989, 72, 1416) (200 mg, 1.1 mmol) and anthracene (178 mg, 1mmol) were suspended in dry toluene (2 ml) and a catalytic amount of anhydrous aluminium chloride was added. The reaction mixture was stirred and refluxed overnight. On cooling a white solid separated which was filtered and washed successively with toluene and pentane and air dried. The solid was then taken up in ethyl acetate and washed with dilute HCl and brine and finally dried and evaporated to leave a white solid (185 mg, 62%)

b. Alkylation of the Diels-Alder adduct

The product from step a (312 mg, 1 mmol), anhydrous potassium carbonate (138 mg, 1 mmol) and 2-bromomethylnaphthalene (225 mg, 1 mmol) were dissolved in dry DMF (3 ml) and stirred and heated to 100° for 4h. After cooling the solution was poured onto cold water (30 ml) and the resulting white solid filtered off and dried in an oven. The solid was triturated with hexane/toluene/ethanol 9:9:2 and the solid was recrystallised from ethanol (178 mg, 39%), m.p. 184-5°

c. 8-(2-naphthylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7-sulphonic acid

Sodium (16 mg, 0.7 mmol) was dissolved in methanol (5 ml) and the product from step b was added (225 mg, 0.5 mmol). The reaction was stirred and refluxed for 1h. The reaction mixture was cooled and acidified with concentrated HCl. The reaction mixture was then evaporated and the residue partitioned between water and ethyl acetate. The organic layer was dried and evaporated. The product was recrystallised from chloroform. Yield 152 mg, 32%, m.p. 245-7° found: C, 68.74; H, 4.88; N, 2.83. $C_{25}H_{23}NO_4S$. 1.0 H_2O requires C, 68.97; H, 5.16; N, 2.87%

Example 19 Preparation of (±)-cis-8-(phenylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-sulphonic acid

This was prepared essentially as in example 18 using benzyl bromide in step b instead of 2-bromomethylnaphthalene m.p. 245-7° found: C, 68.764; H, 4.81; N, 3.19. $C_{24}H_{21}NO_4S$ requires C, 68.72; H, 5.05; N, 3.34%

Example 20 Preparation of (±)-cis-8-(2-naphthylmethylamino-sulphonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

a. Diels-Alder adduct of anthracene and β-sulphoacrylic anhydride

β-sulphoacrylic anhydride (prepared as in J.A.C.S. 1962, 84, 653) (184 mg, 1.0 mmol) and anthracene (178 mg, 1mmol) were suspended in dry toluene (6 ml) and refluxed under an atmosphere of dry nitrogen for 3h. The reaction mixture was decanted from a small amount of tarry residue and cooled in ice. White crystals that separated were filtered off and washed with a little hexane and dried. Yield 163 mg, 52%

b. (±)-cis-8-(2-naphthylmethylaminosulphonyl)-2,3,5,6-dibenzo-

bicyclo[2.2.2]octane-7-carboxylic acid

The Adduct from step a (207 mg, 0.66 mmole) and 2-naphthylmethylamine (209 mg, 1.33 mmol) were dissolved in dry THF (5 ml) and DMAP (5 mg) was added. The solution was stirred at room temperature overnight and evaporated to dryness. The residue was taken up in methanol and water and stirred with Amberlite IR-120(plus) resin, filtered and evaporated. The residue was triturated with ether, to yield the title compound 215 mg, 68% m.p. 212-15 found: C, 69.78; H, 4.98; N, 2.98. $C_{28}H_{23}NO_4S$. 0.7 H_2O requires C, 69.75; H, 5.10; N, 2.91%

Example 21 Preparation of (±)-cis-8-(2-(3-indolyl)ethylamino-sulphonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

This was prepared essentially as in example 20 but using tryptamine instead of 2-naphthylmethylamine in step b, m.p. >220° found: C, 68.87; H, 5.17; N, 6.07. $C_{27}H_{24}N_2O_4S$ requires C, 68.63; H, 5.12; N, 5.92%

Example 22 Preparation of (±)-cis-8-(1-adamantylmethylamino-sulphonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

This was prepared essentially as in example 21 but using 1-adamantylmethylamine instead of 2-naphthylmethylamine in step b, m.p. 135-40° found: C, 69.90; H, 6.49; N, 2.68. $C_{28}H_{31}NO_4S$. 0.2H_2O requires C, 69.89; H, 6.58; N, 2.91%

Example 23 Preparation of cis-7-(1-R-carboxy-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

(±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid (prepared as in example 14) (440 mg, 1 mmole) was dissolved by warming in dry DMF (10 ml). Isopropenylsuccinimido carbonate (200 mg, 1 mmole) was then added

at room temperature. A catalytic amount of DMAP was added and the reagents stirred for 4h. Triethylamine (0.168 ml, 1.2 mmole) was added followed by D-alanine (100 mg, 1.1 mmole) and the reaction left to stir at room temperature for 60h. The reaction mixture was poured onto 2N HCl and the white precipitate so formed was isolated by filtration. The solid was further purified by column chromatography (silica, dichloromethane to 90% dichloromethane and 10% methanol) to leave the title compound (50 mg). The compound was characterised and tested as the N-methyl-D-glucamine salt m.p 128-30°, found: C, 61.98; H, 7.42; N, 5.85. $C_{39}H_{53}N_3O_9$. $2.4H_2O$ requires C, 62.32; H, 7.75; N, 5.59%

Example 24 Preparation of cis-(±)-7-(2-methoxycarbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

This was prepared essentially as in example 23 using beta-alanine methyl ester instead of D-alanine, m.p. 207°, found: C, 74.98; H, 7.46; N, 5.27. $C_{33}H_{38}N_2O_4$ requires C, 75.26; H, 7.27; N, 5.32%.

Example 25 Preparation of cis-7-(1-S-methoxycarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

(±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid (prepared as in example 14) (440 mg, 1 mmole) and PyBOP (520 mg, 1 mmole) were taken up in dry dichloromethane (15 ml) and Hunigs base (0.52 ml, 3 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. L-alanine methyl ester hydrochloride (140 mg, 1 mmole) was added and the mixture stirred overnight. The organic layer was washed with 5% potassium hydrogensulphate (15 ml), sodium hydrogencarbonate (15 ml) and saturated brine (15 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography on silica using 80% ethyl acetate and 20% hexane as eluent. The title compound

(300 mg, 57%) was isolated as a white solid, m.p. 107°, found: C, 75.33; H, 7.25; N, 5.16. $C_{33}H_{38}N_2O_4$ requires C, 75.26; H, 7.27; N, 5.32%

Example 26 Preparation of cis-7-(1-S-methoxycarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (diastereomer A)

The compound of example 25 was separated into its component diastereomers by preparative HPLC using a silica phase column and 50% ethyl acetate and 50% hexane as eluant. The title compound diastereomer A had a retention time of 18.4 minutes and was isolated as a white powder, m.p.95-100°, $[\alpha]^D$= -10.5° (c= 1.66 in methanol), found: C, 75.32; H, 7.14; N, 5.33. $C_{33}H_{38}N_2O_4$ requires C, 75.26; H, 7.27; N, 5.32%

Example 27 Preparation of cis-7-(1-S-methoxycarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (diastereomer B)

The compound of this example was the second diastereomer isolated by the HPLC technique described in example 26. The title compound diastereomer B had a retention time of 21.7 minutes and was isolated as a white powder, m.p.75-85°, $[\alpha]^D$= +3.8° (c= 1.57 in methanol), found: C, 73.41; H, 7.37; N, 5.20. $C_{33}H_{38}N_2O_4$. 0.73 H_2O requires C, 73.42; H, 7.37; N, 5.20%

Example 28 Preparation of cis-7-(1-R-methoxycarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 25 but using D-alanine methyl ester hydrochloride instead of the L-isomer. The title compound (300 mg, 57%) was isolated as a white solid, m.p. 113-5°, found: C, 74.41; H, 7.42; N, 5.14. $C_{33}H_{38}N_2O_4$.0.33 H_2O

requires C, 74.41; H, 7.32; N, 5.26%

Example 29 Preparation of cis-(±)-7-(2-benzyloxycarbonyl-ethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 25 but using the benzyl ester of beta alanine instead of L-alanine methyl ester hydrochloride. Yield 70%, m.p. 77-8°, found: C, 76.67; H, 7.04; N, 4.52. $C_{39}H_{42}N_2O_4.0.43\ H_2O$ requires C, 76.73; H, 7.08; N, 4.59%

Example 30 Preparation of cis-(±)-7-(2-carboxy-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane

The product of example 29 (370 mg, 0.6 mmole) was dissolved in ethanol (20 ml) and 10% palladium on charcoal (100 mg) was added. The mixture was stirred under an atmosphere of hydrogen overnight. The product was filtered through celite and on evaporation yielded the title compound, 56%. The product was characterised and tested as the N-methyl-D-glucamine salt, m.p. 75-8°, found: C, 62.54; H, 7.94; N, 5.31. $C_{39}H_{53}N_3O_9$. 2.44 H_2O requires C, 62.31; H, 7.76; N, 5.59%.

Example 31 Preparation of cis-7-(1-S-aminocarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 25 but using L-alaninamide hydrochloride instead of the L-alanine methyl ester hydrochloride. Yield 81%, m.p. 175-185°, $[\alpha]^D$= -6.5° (c=1 in methanol), found: C, 73.13; H, 7.53; N, 7.95. $C_{32}H_{37}N_3O_3$. 0.76 H_2O requires C, 73.16; H, 7.39; N, 8.00%

Example 32 Preparation of cis-7-(1-S-(hydroxymethyl)-ethyl-

aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 25 but using L-alaninol instead of the L-alanine methyl ester hydrochloride. Yield 76%, m.p. 115-120°, $[\alpha]^D$= -4.0° (c=1 in methanol), found: C, 73.09; H, 7.82; N, 5.32. $C_{32}H_{38}N_2O_3$. 1.5 H_2O requires C, 73.14; H, 7.86; N, 5.33%

Example 33 Preparation of cis-7-(1-S-benzyloxycarbonyl-ethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer A)

The reaction was performed essentially as in example 25 but using the L-alanine benzyl ester of instead of L-alanine methyl ester hydrochloride. Overall yield 62%, The two diastereomers were separated by column chromatography (silica eluant 93% dichloromethane and 7% ethyl acetate). The less polar isomer has been designated diastereomer A, the title compound, Retention time HPLC silica 50% hexane and 50% ethyl acetate 7.9 min, m.p. 92-4°, $[\alpha]^D$= -5.0° (c=1 in chloroform), found: C, 75.49; H, 7.12; N, 4.40. $C_{39}H_{42}N_2O_4$.1.0 H_2O requires C, 75.39; H, 7.15; N, 4.51%

Example 34 Preparation of cis-7-(1-S-benzyloxycarbonyl-ethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer B)

The more polar isomer from the chromatographic separation outlined in example 33 was designated diastereomer B, Retention time HPLC silica 50% hexane and 50% ethyl acetate 10.9 min, m.p. 90-5°, $[\alpha]^D$= -1.0° (c=1 in chloroform), found: C, 77.66; H, 7.24; N, 4.41. $C_{39}H_{42}N_2O_4$ requires C, 77.71; H, 7.02; N, 4.65%

Example 35 Preparation of cis-7-(1-S-carboxyethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-

dibenzobicyclo[2.2.2]octane (diastereomer A)

The compound was prepared essentially as described in example 30 but using the product of example 33 instead of cis-(±)-7-(2-benzyloxycarbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (the product of example 29) as the substrate. Yield 87%, $[\alpha]^D$= -16.0° (c=1 in methanol). The compound was further characterised and tested as the N-methyl-D-glucamine salt, m.p. 100-105°, found: C, 60.66; H, 7.82; N, 5.74. $C_{39}H_{53}N_3O_6$. 3.4 H_2O requires C, 60.93; H, 7.84; N, 5.47%.

Example 36 Preparation of cis-7-(1-S-carboxyethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer B)

The compound was prepared essentially as described in example 30 but using the product of example 34 instead of cis-(±)-7-(2-benzyloxycarbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (the product of example 29) as the substrate. Yield 99%, $[\alpha]^D$= +3.5° (c=1 in methanol). The compound was further characterised and tested as the N-methyl-D-glucamine salt, m.p. 105-110°, found: C, 61.89; H, 7.67; N, 5.72. $C_{39}H_{53}N_3O_6$. 2.6 H_2O requires C, 62.03; H, 7.77; N, 5.57%.

Example 37 Preparation of endo-cis-(±)-8-(1-adamantyl-methylaminocarbonyl)-2,3-benzo-5,6-(2,5-dimethoxybenzo)-bicyclo[2.2.2]octane-7-carboxylic acid

a. Diels-Alder adduct of 1,4-dimethoxyanthracene

Maleic anhydride (0.21 g, 2.18 mmole) and 1,4-dimethoxyanthracene (0.52 g, 2.18 mmole) were dissolved in toluene (5 ml) and heated to reflux for 4h under an atmosphere of argon. The solvent was evaporated and the residue washed with dichloromethane affording

a white powder which was recrystallised from acetone to yield the exo adduct (140 mg), used in the preparation of example 38. The endo adduct was obtained as a white solid on addition of hexane to the dichloromethane solution, which was filtered and dried (143 mg).

b. endo-cis-(±)-8-(1-adamantylmethylaminocarbonyl)-2,3-benzo-5,6-(2,5-dimethoxybenzo)bicyclo[2.2.2]octane-7-carboxylic acid

The endo adduct (from step a) (132 mg, 0.39 mmole) was dissolved in THF (3 ml) and 1-adamantylmethylamine (70 mg, 0.39 mmole) was added. The reaction was stirred at room temperature under an atmosphere of argon for 15 min. The solution was evaporated and taken up in dichloromethane and precipitated with hexane. The solution was filtered and dried, dissolved in warm ether and decanted from insoluble material. Addition of hexane, cooling and filtration gave the title compound (93 mg, 48%). The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 99-103°, found: C, 61.63; H, 7.73; N, 3.92. $C_{38}H_{52}N_2O_{10}$. 2.3 H_2O requires C, 61.76; H, 7.73; N, 3.79%.

Example 38 Preparation of exo-cis-(±)-8-(1-adamantylmethylaminocarbonyl)-2,3-benzo-5,6-(2,5-dimethoxybenzo)bicyclo-[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 37 step b but using the exo anhydride from example 37, step a, rather than the endo isomer. Yield 88%. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 109-112°, found: C, 63.07; H, 7.70; N, 3.71. $C_{38}H_{52}N_2O_{10}$. 1.5 H_2O requires C, 63.04; H, 7.66; N, 3.87%.

Example 39 Preparation of cis-(±)-8-(2-adamantylmethylaminocarbonyl)-2,3-benzo-5,6-(2,5-dimethoxybenzo)bicyclo-[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 1 step b using 2-adamantylmethylamine instead of 1-phenyl-3-propylamine. Yield 85%. The compound was characterised and tested as the N-methyl-D-glucamine salt, found: C, 67.73; H, 7.81; N, 4.41. $C_{36}H_{48}N_2O_8$ requires C, 67.90; H, 7.60; N, 4.40%.

Example 40 Preparation of cis-7-(1-S-dimethylamino-carbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 25 but using L-alanine-N,N-dimethylamide trifluoroacetate instead of the L-alanine methyl ester hydrochloride. Yield 79%, m.p. 130-5°, $[\alpha]^D$= -14° (c=1 in methanol) found: C, 72.58; H, 7.86; N, 7.35. $C_{34}H_{41}N_3O_3$. 1.3 H_2O requires C, 72.49; H, 7.81; N, 7.46%

Example 41 Preparation of cis-7-(1-S-methoxycarbonyl-ethylaminocarbonyl)-8-(cyclohexylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 25 but using (±)-cis-8-(1-cyclohexylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid (prepared in example 9) instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid. Yield 59%, m.p. 80-2°, found: C, 73.10; H, 7.31; N, 5.78. $C_{29}H_{34}N_2O_4$ requires C, 73.39; H, 7.22; N, 5.90%

Example 42 Preparation of cis-7-[methoxycarbonylmethyl-(N-methyl)-aminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 25 but using the methyl ester of sarcosine hydrochloride instead of the L-alanine methyl ester hydrochloride. Yield 74%, m.p. 185-7°,

found: C, 75.47; H, 7.33; N, 5.22. $C_{33}H_{38}N_2O_4$ requires C, 75.26; H, 7.27; N, 5.32%

Example 43 Preparation of cis-7-[ethoxycarbonylmethyl-(N-methyl)-aminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 25 but using the ethyl ester of sarcosine hydrochloride instead of the L-alanine methyl ester hydrochloride. Yield 57%, found: C, 75.40; H, 7.51; N, 5.03. $C_{34}H_{40}N_2O_4$ requires C, 75.53; H, 7.46; N, 5.18%

Example 44 Preparation of (±)-trans-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

a. (±)-trans-8-ethoxycarbonyl-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7-carboxylic acid

Anthracene (5 g, 28 mmol) and fumaric acid monoethyl ester (4.04 g, 28 mmol) were dissolved in dioxan (50 ml) and the solution heated at reflux for 3d. The reaction mixture was evaporated and the solid obtained recrystallised from hot toluene and dried (5.06 g, 56%).

b. (±)-trans-ethyl-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylate

The product of step a (0.2 g, 0.62 mmol) was stirred in anhydrous benzene (25 ml) and thionyl chloride (0.27 ml, 3.1 mmol) was added. The mixture was stirred at room temperature for 2h. The solution was evaporated in vacuo to leave a gum. This was taken up in dry dichloromethane (25 ml) and 1-adamantylmethylamine (0.103 g, 0.62 mmol) was added followed by triethylamine (0.095 0ml, 0.68 mmol) and the mixture stirred at room temperature for 1h. The dichloromethane solution was washed successively with 2M

hydrochloric acid, water and saturated brine and dried, filtered and evaporated to afford a colourless solid (0.28 g, 96%).

c. (±)-trans-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The product of step b (0.28 g, 0.6 mmol) was dissolved in ethanol (20 ml) and sodium hydroxide (48 mg, 1.2 mmole) was added. The reaction mixture was heated to reflux for 2 min whereupon it was diluted with 2N hydrochloric acid, cooled to room temperature and filtered. The precipitated solid was washed successively with water, ethanol (2 ml), ether (10 ml) and dried (165 mg, 63%). The compound was characterised and tested as the N-methyl-D-glucamine salt, found: C, 67.73; H, 7.62; N, 4.22. $C_{36}H_{48}N_2O_8$ requires C, 67.90; H, 7.60; N, 4.40%.

Example 45 Preparation of methyl cis-(±)-8-(1-adamantylmethyloxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylate

cis-(±)-8-(1-adamantylmethyloxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid prepared as in example 13 (115 mg, 0.26 mmol) was dissolved in ether (10 ml) and a solution of diazomethane in ether was added dropwise until a yellow colour persisted in solution. After 20 min at room temperature the reaction was quenched by dropwise addition of acetic acid. The reaction mixture was diluted with ether and washed sequentially with 5% sodium hydrogencarbonate solution and brine. The organic layer was dried, filtered and evaporated to give a colourless glass. Trituration with hexane then gave the desired product as a white solid (65 mg, 55%), m.p. 186-7°, found: C, 78.86; H, 7.06. $C_{30}H_{32}O_4$ requires C, 78.92; H, 7.06%

Example 46 Preparation of cis-7-(2-R-benzyloxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

(±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid (prepared as in example 14) (440 mg, 1 mmole) and PyBOP (520 mg, 1 mmole) were taken up in dry dichloromethane (15 ml) and Hunigs base (0.52 ml, 3 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. D-Proline benzyl ester hydrochloride (266 mg, 1.1 mmole) was added and the mixture stirred overnight. The organic layer was washed with 5% potassium hydrogensulphate (15 ml), sodium hydrogencarbonate (15 ml) and saturated brine (15 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography on silica using a gradient elution starting with 50% ethyl acetate and 50% hexane going up to 80% ethyl acetate and 20% hexane. The title compound (580 mg, 92%) was isolated, m.p. 89-90°, found: C, 78.14; H, 7.13; N, 4.41. $C_{41}H_{44}N_2O_4$ requires C, 78.31; H, 7.05; N, 4.45%

Example 47 Preparation of cis-7-(2-S-benzyloxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This compound was prepared essentially as in example 46 using L-proline benzyl ester hydrochloride instead of D-proline benzyl ester hydrochloride. m.p. 91-2°, found: C, 77.03; H, 7.12; N, 4.22. $C_{41}H_{44}N_2O_4$. 0.6 H_2O requires C, 76.99; H, 7.12; N, 4.38%

Example 48 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

The product of example 46 (520 mg, 0.83 mmol) was dissolved in ethanol (20 ml) and 10% palladium on charcoal (100 mg) was added. The reaction mixture was stirred overnight under an atmosphere of hydrogen and then filtered through celite and evaporated to yield the title compound (380 mg, 86%). The compound was characterised and tested as the N-methyl-D-glucamine salt m.p. 124-7°, found: C,

64.58; H, 7.92; N, 5.38. $C_{41}H_{55}N_3O_9$. 1.71 H_2O requires C, 64.40; H, 7.70; N, 5.45%

Example 49 Preparation of cis-7-(2-S-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This compound was prepared essentially as in example 48 but using the product of example 47 as substrate rather than the product of example 46. Yield 60% The compound was characterised and tested as the N-methyl-D-glucamine salt m.p. 98-101°, found: C, 61.12; H, 8.11; N, 5.08. $C_{41}H_{55}N_3O_9$. 3.88 H_2O requires C, 61.26; H, 7.87; N, 5.23%

Example 50 Preparation of cis-7-(2-methoxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound of example 46 (320 mg, 0.59 mmol) was dissolved in dioxan (10 ml) and a solution of diazomethane in ether was added dropwise until the colour persisted. After stirring for 1h at room temperature acetic acid was added to quench the reaction and the solution was evaporated and taken up in ethyl acetate. The product was then washed with saturated sodium hydrogencarbonate solution and saturated brine. The organic phase was dried filtered and evaporated and the title compound purified on silica using 50% ethyl acetate and 50% hexane as eluent. Yield (120 mg, 37%), m.p. 112-5°, found: C, 75.86; H, 7.43; N, 4.96. $C_{35}H_{40}N_2O_4$ requires C, 75.86; H, 7.29; N, 5.07%

Example 51 Preparation of cis-7-(2-S-methoxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This compound was prepared essentially as in example 50 using the

compound of example 47 as substrate instead of the compound of example 46. Yield 43%, m.p. 104-6°, found: C, 74.55; H, 7.43; N, 4.88. $C_{35}H_{40}N_2O_4$. 0.6 H_2O requires C, 74.57; H, 7.37; N, 4.97%

Example 52 Preparation of (±)-cis-7-(3-indolylethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

(±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid (prepared as in example 14) (440 mg, 1 mmole) and PyBOP (520 mg, 1 mmole) were taken up in dry dichloromethane (15 ml) and Hunigs base (0.52 ml, 3 mmole) was added. The reaction mixture was stirred under an atmosphere of dry argon for 1h. Tryptamine hydrochloride (197 mg, 1 mmole) was added and the mixture stirred overnight. The organic layer was washed with 5% potassium hydrogensulphate (15 ml), sodium hydrogencarbonate (15 ml) and saturated brine (15 ml). It was then dried, filtered and evaporated to leave the crude title compound which was further purified by column chromatography on silica using 15% ethyl acetate and 85% dichloromethane as eluent. The title compound (432 mg, 74%) was isolated as a white solid, m.p. 130-40°, found: C, 75.92; H, 6.98; N, 7.19. $C_{50}H_{41}N_3O_2$ requires C, 76.26; H, 7.28; N, 6.84%

Example 53 Preparation of cis-7-[R-2-(3-indolyl)-1-methoxy-carbonyl-ethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This compound was prepared essentially as in example 52 using D-tryptophan methyl ester hydrochloride instead of tryptamine hydrochloride. Yield 78%, m.p. 135-40°; found: C, 75.64; H, 6.81; N, 6.09. $C_{41}H_{43}N_3O_4$. 0.65 H_2O requires C, 75.35; H, 6.83; N, 6.43%

Example 54 Preparation of cis-7-[2-S-(3-indolyl)-1-methoxy-carbonyl-ethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-

2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This compound was prepared essentially as in example 52 using L-tryptophan methyl ester hydrochloride instead of tryptamine hydrochloride. Yield 80%, m.p. 135-42°, found: C, 76.55; H, 6.95; N, 6.77. $C_{41}H_{43}N_3O_4$ requires C, 76.63; H, 6.75; N, 6.55%

Example 55 Preparation of cis-7-[2-R-(3-indolyl)-1-carboxy-ethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

a. cis-7-[2-R-(3-indolyl)-1-benzyloxycarbonyl-ethylamino-carbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane and separation of diastereomers

The mixture of diastereomers was prepared essentially as in example 52 using D-tryptophan benzyl ester trifluoroacetate salt instead of tryptamine hydrochloride. The diastereomers were separated by column chromatography (silica 15% ethyl acetate and 85% dichloromethane) to give a 35% yield of each component.

b. cis-7-[2-R-(3-indolyl)-1-carboxy-ethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (diastereomer 1)

Diastereomer 1 (from step a) (0.23 g, 0.32 mmol) was dissolved in methanol (10 ml) and a catalytic amount of 10% palladium on charcoal was added. The mixure was stirred under an atmosphere of hydrogen overnight, filtered and evaporated to leave the title compound (0.21 g, 100%). The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 130-5°, $[\alpha]^D$= -18.5° (c=1 in methanol), found: C, 67.17; H, 7.36; N, 6.49. $C_{47}H_{58}N_4O_9 . H_2O$ requires C, 67.09; H, 7.19; N, 6.65%

Example 56 Preparation of cis-7-[2-R-(3-indolyl)-1-carboxy-ethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-

2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 4 but using diastereomer 2 (isolated in example 4 step a) instead of diastereomer 1 in step b. Yield 90% The compound was further characterised and tested as the N-methyl-D-glucamine salt, m.p. 140-5°, $[\alpha]^D$= -22.0° (c=1 in methanol), found: C, 67.16; H, 7.18; N, 6.68. $C_{47}H_{58}N_4O_9$. H_2O requires C, 67.09; H, 7.19; N, 6.65%

Example 57 Preparation of cis-7-[2-S-(3-indolyl)-1-carboxyethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

This was prepared essentially as in example 55 but using L-tryptophan benzyl ester trifluoracetate instead of the D-isomer in step a. Separation of diastereomers was achieved at the benzyl ester stage as indicated in example 55 step a. and diastereomer 1 used in step b. was again the isomer with the higher R_f. Overall yield 22% based on starting racemic carboxylic acid.

The compound was further characterised and tested as the N-methyl-D-glucamine salt, m.p. 119-24°, $[\alpha]^D$= -5.7° (c=0.7 in methanol), found: C, 65.07; H, 7.25; N, 6.44. $C_{47}H_{58}N_4O_9$ requires C, 65.03; H, 7.32; N, 6.45%

Example 58 Preparation of cis-7-[2-S-(3-indolyl)-1-carboxyethylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane Diastereomer 2

The compound was prepared essentially as in example 55 but using diastereomer 2 (isolated in example 57 step a) instead of diastereomer 1 in step b. Overall yield 26% based on starting racemic carboxylic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 133-8°, $[\alpha]^D$= +7.6° (c=0.66 in methanol), found: C, 64.42; H, 7.17; N, 6.41. $C_{47}H_{58}N_4O_9.3H_2O$ requires C, 64.37; H, 7.35; N, 6.39%

Example 59 Preparation of cis-(±)-7-(2-Furanylmethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in Example 25 but using furfurylamine instead of L-alanine methyl ester hydrochloride. Yield 65%, m.p. 300°, found: C, 78.15; H, 6.99; N, 5.42. $C_{34}H_{36}N_2O_3$ requires C, 78.43; H, 6.97; N, 5.38%

Example 60 Preparation of cis-(±)-7-[2-(5-methyloxycarbonyl)-furanylaminocarbonyl]-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in Example 25 but using 5-methoxycarbonyl-2-aminofuran instead of L-alanine methyl ester hydrochloride. Yield 65%, m.p. 225°, found: C, 74.31; H. 6.54; N, 4.91. $C_{35}H_{36}N_2O_5$ requires C, 74.45; H, 6.43; N, 4.96%

Example 61 Preparation of cis-7-(1-S-benzyloxycarbonyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the p-toluenesulphonate salt of the benzyl ester of L-valine instead of D-proline benzyl ester hydrochloride. m.p 85-87°. Found: C, 77.99; H, 7.52; N, 4.17. $C_{41}H_{4\text{-}}N_2O_4$. $0.1H_2O$ requires C, 77.86; H, 7.36; N, 4.42%

Example 62 Preparation of cis-7-(1-S-carboxy-2-methyl-propylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 48 but using

the product of example 61 as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt m.p 105-8°. Found: C, 64.00; H, 8.06; N, 5.37. $C_{41}H_{57}N_3O_9$. $1.8H_2O$ requires C, 64.09; H, 7.95; N, 5.46%

Example 63 Preparation of cis-7-(1-S-methoxycarbonyl-2-methyl-propylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers) (150 mg) prepared as in example 62 was dissolved in ethyl acetate (5ml) and a solution of diazomethane in diethyl ether was added until a yellow colour persisted in solution. After stirring the rection mixture at room temperature for 10 min, glacial acetic acid was added and the organic layer was washed with saturated sodium hydrogencarbonate solution, dried over magnesium sulphate, filtered and evaporated. Yield 130 mg, 85%, m.p. 103-5°. Found: C, 75.51; H, 7.67; N, 5.06. $C_{35}H_{42}N_2O_4$ requires C, 75.78; H, 7.63; N, 5.05%

Example 64 Preparation of cis-7-(1-S-2-dicarboxyethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. cis-7-(1-S-2-dibenzyloxycarbonylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the dibenzyl ester of L-aspartic acid instead of D-proline benzyl ester hydrochloride. The product was used directly in step b.

b. cis-7-(1-S-2-dicarboxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 48 but using the product of step a. as substrate instead of the product of example 46. The compound was characterised and tested as the mono-N-methyl-D-glucamine salt, m.p 115-7°. Found: C, 62.84; H, 7.03; N, 5.35. $C_{40}H_{53}N_3O_{11}$. $0.62H_2O$ requires C, 62.54; H, 7.03; N, 5.61%

Example 65 Preparation of 7-(1-S-carboxy-2-phenyl-ethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of phenylalanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 101-3°. Found: C, 66.13; H, 7.64; N, 5.05. $C_{45}H_{57}N_3O_8$. $1.9H_2O$ requires C, 66.06; H, 7.49; N, 5.14%

Example 66 Preparation of (±)-cis-7-(1-methoxycarbonyl-1-methyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 46 but using the trifluoromethylacetate salt of the methyl ester of aminoisobutyric acid instead of D-proline benzyl ester hydrochloride. m.p 120-2°. Found: C, 75.51; H, 7.43; N, 4.90. $C_{34}H_{40}N_2O_4$ requires C, 75.53; H, 7.46; N, 5.18%

Example 67 Preparation of (±)-cis-7-(1-carboxy-1-methyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 64 but using the benzyl ester of aminoisobutyric acid in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 115-25°. Found:

C, 64.71; H, 7.74; N, 5.92. $C_{40}H_{55}N_3O_9$ requires C, 64.93; H, 7.76; N, 5.68%

Example 68 Preparation of cis-7-(2-R-carboxy-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of cis hydroxy-D-proline in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 118-21°. Found: C, 58.59; H, 7.48; N, 5.10. $C_{41}H_{55}N_3O_{10}$. 4.8 mol H_2O requires C, 58.89; H, 7.78; N, 5.02%

Example 69 Preparation of cis-7-(2-R-carboxy-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The cis-7-(2-R-benzyloxycarbonyl-4-R-hydroxy-pyrrolidino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane mixture of diastereomers prepared as referenced in example 68 was separated into its two diastereomeric components by repeated recrystallisation from ethyl acetate. The insoluble isomer was designated diastereomer 1. The soluble material isolated by evaporation was designated diastereomer 2. Diastereomer 1 was converted to the title compound essentially as in example 48 using it as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 112-4°. Found: C, 60.81; H, 7.86; N, 4.96. $C_{41}H_{55}N_3O_{10}$. 4.4 mol H_2O requires C, 60.70; H, 7.68; N, 5.18%

Example 70 Preparation of cis-7-(2-R-carboxy-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

Diastereomer 2 prepared as described in example 69 was converted to the title compound essentially as in example 48 using it as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 132-35°. Found: C, 63.69; H, 7.51; N, 5.04. $C_{41}H_{55}N_3O_{10}$. 1.5 mol H_2O requires C, 63.40; H, 7.52; N, 5.41%

Example 71 Preparation of cis-7-(2-R-methoxycarbonyl-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 63 but using the product of example 69 as substrate instead of cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers), m.p 133-35°. Found: C, 72.81; H, 7.21; N, 4.88. $C_{35}H_{40}N_2O_5$. 0.5 mol H_2O requires C, 72.81; H, 7.15; N, 4.85%

Example 72 Preparation of cis-7-(2-R-methoxycarbonyl-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 63 but using the product of example 70 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers), m.p 133-35°. Found: C, 70.28; H, 7.14; N, 4.81. $C_{35}H_{40}N_2O_5$. 1.5 mol H_2O requires C, 70.42; H, 7.28; N, 4.69%

Example 73 Preparation of (±)-cis-7-(3-(±)-carboxy-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 46 but using the trifluoromethylacetate salt of the benzyl ester of racemic

nipecotic acid instead of D-proline benzyl ester hydrochloride. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.54; H, 8.12; N, 5.23. $C_{42}H_{57}N_3O_9$. 1.4 H_2O requires C, 65.24; H, 7.80; N, 5.43%

Example 74 Preparation of (±)-cis-7-(3-(±)-methoxycarbonyl-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 63 but using the product of example 73 as substrate instead of cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers). Found: C, 74.24; H, 7.30; N, 4.65. $C_{36}H_{42}N_2O_4$. 0.8 H_2O requires C, 74.40; H, 7.56; N, 4.82%

Example 75 Preparation of cis-7-(1-S-cyanoethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound of example 31 (0.33 g, 0.59 mmol) was dissolved in pyridine (5 ml) and cooled to 0° under an atmosphere of dry argon. Tosyl chloride (0.13 g, 0.70 mmol) was added and the reaction allowed to warm to room temperature and was then stirred overnight. The solvent was removed by evaporation and the residue partitioned between ethyl acetate and water. The organic phase was washed successively with 1M hydrochloric acid and saturated sodium hydrogen carbonate solution, dried, filtered and evaporated to leave the crude product. This material was purified by column chromatography (silica, 90% dichloromethane and 10% ethyl acetate) to leave the title compound (150 mg), m.p. 125-8°. Found: C, 76.30; H, 7.23; N, 8.21. $C_{32}H_{35}N_3O_2$. 0.6 H_2O requires C, 76.19; H, 7.23; N, 8.32%

Example 76 Preparation of cis-7-(1-S-methylcarbonyl-

ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound of example 75 (0.25 g, 0.5 mmol) was dissolved in THF (3 ml) and cooled to 0° under an atmosphere of dry argon. Methyl magnesium bromide solution (1.4M in THF 1.4 ml, 2.0 mmol) was added. The solution was stirred at 0° for 1h. 2M hydrochloric acid (2ml) was added followed by saturated ammonium chloride solution. (20 ml). The product was extracted with ethyl acetate (2 x 20 ml), dried, filtered and evaporated (0.25 ml). The crude product was purified by column chromatography (silica 90% dichloromethane and 10% ethyl acetate) to leave the title compound (130 mg), m.p. 105-10°. Found: C, 76.61; H, 7.40; N, 5.25. C33H38N2O3. 0.4 H2O requires C, 76.54; H, 7.55; N, 5.41%

Example 77 Preparation of cis-7-(1-S-propyloxycarbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the trifluoromethylacetate salt of the propyl ester of L-alanine (prepared from alklation of the caesium salt of BOC-L-alanine with propyl bromide followed by treatment with trifluoroacetic acid) instead of D-proline benzyl ester hydrochloride. m.p 90-3°. Found: C, 75.33; H, 7.74; N, 4.81. $C_{35}H_{42}N_2O_4$. 0.25 H_2O requires C, 75.33; H, 7.66; N, 5.01%

Example 78 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound of example 48 was separated into its constituent diastereomers by reverse phase HPLC (silica C8 column 60% acetonitrile, 40% water and 0.1% acetic acid modifier). The first compound eluted was designated diastereomer 1, the title compound. The compound was characterised and tested as the N-methyl-D-

glucamine salt. Found: C, 64.23; H, 7.86; N, 5.38. $C_{41}H_{55}N_3O_{10}$. 1.8 H_2O requires C, 64.22; H, 7.71; N, 5.48%

Example 79 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The second compound eluted during the HPLC separation referred to in example 78 was designated diastereomer 2. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.23; H, 7.86; N, 5.38. $C_{41}H_{55}N_3O_{10}$. 1.8 H_2O requires C, 64.22; H, 7.71; N, 5.48%

Example 80 Preparation of cis-7-(2-S-methoxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound of example 51 was separated into its constituent diastereomers by repeated recrystallisation from 80% ethyl acetate and 20% hexane. The crystals isolated were designated diastereomer 1, the title compound, m.p. 256°. Found: C, 76.01; H, 7.31; N, 4.98. $C_{35}H_{40}N_2O_4$ requires C, 76.06; H, 7.29; N, 5.07%

Example 81 Preparation of cis-7-(2-S-methoxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The mother liquors from the recrystallisation described in example 80 were concentrated to yield the other pure isomer designated diastereomer 2, m.p. 94-6°. Found: C, 74.88; H, 7.31; N, 5.03. $C_{35}H_{40}N_2O_4$. 0.5 H_2O requires C, 74.91; H, 7.35; N, 4.99%

Example 82 Preparation of cis-7-(1-S-carboxy-2-hydroxyethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-

dibenzobicyclo[2.2.2]octane (diastereomer 1)

Step a. cis-7-(1-S-Benzyloxycarbonyl-2-hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1 and 2)

The reaction was performed essentially as in example 46 but using L-serine benzyl ester hydrochloride instead of D-proline benzyl ester hydrochloride. The compound was separated into its component diastereomers by column chromatography (silica 25% ethyl acetate and 75% dichloromethane). The less polar material was designated diastereomer 1 and the more polar diastereomer 2.

Step b. cis-7-(1-S-carboxy-2-hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The reaction was performed essentially as in example 48 but using the diastereomer 1 from step a. above as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 102-5° found: C, 61.24; H, 7.78; N, 5.22. $C_{30}H_{53}N_3O_{10}$. 2.4 H_2O requires C, 61.08; H, 7.59; N, 5.48%

Example 83 Preparation of cis-7-(1-S-carboxy-2-hydroxy-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The reaction was performed essentially as in example 48 but using the diastereomer 2 from example 82 step a. as substrate instead of the product of example 46. The compound was characterised and tested and tested as the N-methyl-D-glucamine salt, m.p 107-10° found: C, 61.27; H, 7.69; N, 5.29. $C_{30}H_{53}N_3O_{10}$. 2.3 H_2O requires C, 61.19; H, 7.59; N, 5.49%

Example 84 Preparation of cis-7-(1-S-methoxycarbonyl-2-

hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

Step a. cis-7-(1-S-methoxycarbonyl-2-hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using L-serine methyl ester hydrochloride instead of D-proline benzyl ester hydrochloride.

Step b. cis-7-(1-S-methoxycarbonyl-2-hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (diastereomer 1)

The compound prepared in step a. was separated into its component diastereomers by column chromatography (silica 30% ethyl acetate and 70% dichloromethane). The less polar material was designated diastereomer 1, the title compound, m.p 115-20° found: C, 68.94; H, 6.95; N, 4.91. $C_{33}H_{38}N_2O_5$. 1.6 H_2O requires C, 69.26; H, 7.27; N, 4.90%

Example 85 Preparation of cis-7-(1-S-methoxycarbonyl-2-hydroxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound of this example was the more polar diastereomer isolated from the column chromatography described in example 84 step b, m.p 100-10° found: C, 56.92; H, 6.03; N, 3.49. $C_{33}H_{38}N_2O_5$. 2.4 DCM requires C, 56.91; H, 5.78; N, 3.75%

Example 86 Preparation of (±)- cis-7-(1-methoxycarbonyl-1-ethyleneaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The product of example 64 step a. (270 mg, 0.5 mmol) was dissolved

in THF (2 ml) and N,N-carbonyldiimidazole (80 mg, 0.5 mmol) was added followed by triethylamine (0.07 ml). The solution was stirred at room temperature overnight under an atmosphere of dry argon. The solvent was evaporated and the crude material purified by column chromatography (silica 10% ethyl acetate and 90% dichloromethane) to give the title compound as a solid (50 mg), m.p 98-108° found: C, 73.59; H, 7.05; N, 5.06. $C_{33}H_{36}N_2O_4$. 0.8 H_2O requires C, 73.55; H, 7.03; N, 5.20%

Example 87 Preparation of cis-7-(1-S-methoxycarbonyl-2-carboxyethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the alpha methyl beta benzyl diester of aspartic acid in step a. instead of the dibenzyl ester. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p 103-5° found: C, 56.56; H, 7.70; N, 4.71. $C_{41}H_{55}N_3O_{11}$. 5.9 H_2O requires C, 56.48; H, 7.72; N, 4.82%

Example 88 Preparation of cis-7-(2-R-carboxypiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of D-pipecolinic acid in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.13; H, 8.07; N, 5.64. $C_{42}H_{57}N_3O_9$. 1.5 H_2O requires C, 65.10; H, 7.81; N, 5.42%

Example 89 Preparation of cis-7-(2-R-methoxycarbonylpiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 but using the product of example 88 as substrate instead of cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers). Found: C, 70.00; H, 7.18; N, 4.70. $C_{36}H_{42}N_2O_4$. 0.5 $CHCl_3$ requires C, 70.04; H, 6.78; N, 4.40%

Example 90 Preparation of cis-7-(2-S-methoxycarbonyl-4-S-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the trifluoroacetate salt of the methyl ester of cis-hydroxy-L-proline instead of D-proline benzyl ester hydrochloride. Found: C, 76.36; H, 7.24; N, 4.38. $C_{35}H_{40}N_2O_5$. 0.9 toluene requires C, 76.25; H, 7.31; N, 4.26%

Example 91 Preparation of cis-7-(2-S-methoxycarbonyl-4-R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the trifluoroacetate salt of the methyl ester of trans-hydroxy-L-proline instead of D-proline benzyl ester hydrochloride. Found: C, 75.16; H, 7.32; N, 4.19. $C_{35}H_{40}N_2O_5$. 0.6 toluene requires C, 75.45; H, 7.24; N, 4.49%

Example 92 Preparation of cis-7-(1-S-methoxycarbonyl-2-benzylsulphenylethylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

Step a. cis-7-(1-S-methoxycarbonyl-2-benzylsulphenylethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 46 but using the benzylthioether of L-cysteine methyl ester hydrochloride instead of D-proline benzyl ester hydrochloride.

Step b. cis-7-(1-S-methoxycarbonyl-2-benzylsulphenylethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound prepared in step a. was separated into its component diastereomers by column chromatography (silica 15% ethyl acetate and 85% dichloromethane). The more polar material(R_f 0.4) was designated diastereomer 1, the title compound, m.p. 80-1° found: C, 72.93; H, 6.88; N, 4.08. $C_{40}H_{44}N_2O_4S$. 0.5 H_2O requires C, 73.04; H, 6.89; N, 4.25%

Example 93 Preparation of cis-7-(1-S-methoxycarbonyl-2-benzylsulphenylethylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The less polar material isolated by the chromatography (R_f 0.6) described in example 92 step b. was designated as diastereomer 2, m.p. 85° found: C, 74.03; H, 7.01; N, 4.38. $C_{40}H_{44}N_2O_4S$ requires C, 74.04; H, 6.64; N, 4.32%

Example 94 Preparation of cis-7-(1-S-carboxyethyl-(N-methyl)-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the trifluoroacetate salt of the benzyl ester of N-methyl-L-alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 100-10° found: C, 64.12; H, 7.89; N, 5.71. $C_{40}H_{45}N_3O_9$. 1.5 H_20 requires C, 64.21; H, 7.80; N, 5.62%

Example 95 Preparation of cis-7-(1-R-carboxyethyl-(N-methyl)-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the trifluoroacetate salt of the benzyl ester of N-methyl-D-alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 105-15° found: C, 62.06; H, 7.81; N, 5.55. $C_{40}H_{55}N_3O_9$. 2.8 H_2O requires C, 62.18; H, 7.91; N, 5.44%

Example 96 Preparation of cis-7-(1-S-methoxycarbonylethyl-(N-methyl)-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 63 but using the product of example 94 as substrate instead of cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers), m.p. 96-8° found: C, 75.55; H, 7.68; N, 5.10. $C_{34}H_{40}N_2O_4$ requires C, 75.53; H, 7.46; N, 5.18%

Example 97 Preparation of cis-7-(1-R-methoxycarbonylethyl-(N-methyl)-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 63 but using the product of example 95 as substrate instead of cis-7-(1-S-carboxy-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers), m.p. 95-105° found: C, 75.49; H, 7.53; N, 5.24. $C_{34}H_{40}N_2O_4$ requires C, 75.53; H, 7.46; N, 5.18%

Example 98 Preparation of (±)-cis-7-(pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 64 but using pyrrolidine in step a. instead of the dibenzyl ester of aspartic acid, m.p. 205-7° found: C, 80.15; H, 7.77; N, 5.78. $C_{33}H_{38}N_2O_2$ requires C, 80.12; H, 7.74; N, 5.66%

Example 99 Preparation of (±)-cis-7-(methylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound of example 14 (440 mg, 1 mmol) was dissolved in dichloromethane (15 ml) and diisopropylethylamine (0.52 ml) and PyBOP (520 mg) were added. The solution was stirred for 5-10 min until a clear solution was obtained. Dry methylamine gas was bubbled through the solution for 5 min until this was saturated. The solution was stirred for 1h and then evaporated. The residue was taken up in ethyl acetate and washed successively with 5% aqueous potassium hydrogensulphate solution (2 x 20 ml) saturated sodium hydrogencarbonate solution (20 ml), brine (20 ml), dried, filtered and evaporated to leave a crude product which was purified by column chromatography (silica 70% dichloromethane and 30% ethyl acetate). The title compound was a white solid (240 mg), m.p. 192-3° found: C, 79.15; H, 7.72; N, 5.91. $C_{30}H_{34}N_2O_2$ requires C, 79.26; H, 7.53; N, 6.16%

Example 100 Preparation of (±)-cis-7-(dimethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 99 but using dimethylamine instead of methylamine, m.p. 253-5° found: C, 78.86; H, 7.78; N, 5.67. $C_{31}H_{36}N_2O_2$ requires C, 78.69; H, 7.8 N, 5.92%

Example 101 Preparation of (±)-cis-7-(ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 99 but using ethylamine instead of methylamine, m.p. 200-1° found: C, 79.82; H,

7.67; N, 5.94. $C_{31}H_{36}N_2O_2$ requires C, 79.45; H, 7.74 N, 5.98%

Example 102 Preparation of (±)-cis-7-(1-methylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 99 but using isopropylamine instead of methylamine, m.p. 122-4° found: C, 74.80; H, 7.21; N, 5.38. $C_{32}H_{38}N_2O_2$. 0.4 DCM. 0.1 ethyl acetate requires C, 74.94; H, 7.56 N, 5.33%

Example 103 Preparation of (±)-cis-7-aminocarbonyl-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 99 but using ammonia instead of methylamine, m.p. 238-40° found: C, 78.78; H, 7.45; N, 6.41. $C_{29}H_{32}N_2O_2$ requires C, 79.06; H, 7.32 N, 6.36%

Example 104 Preparation of (±)-cis-7-(2-benzyloxycarbonylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1-cyano-2,3,5,6-dibenzobicyclo[2.2.2]octane (regioisomer 1)

The mixture of regioisomers was prepared essentially as in example 29 but using (±)-cis-8-(1-adamantylmethylaminocarbonyl)-1-cyano-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid. This in turn was made by reaction of 1-adamantanemethylamine with 1-cyano-2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride essentially as in example 14. The anhydride was prepared by reaction of maleic anhydride with 9-cyanoanthracene in refluxing toluene. The regioisomers were separated by preparative HPLC (silica, ethyl acetate 15% and dichloromethane 85%). The less polar regioisomer was designated regioisomer 1, the title compound, m.p. 205-8° found: C, 76.55; H, 6.61; N, 6.68. $C_{40}H_{41}N_3O_4$ requires C,

76.53; H, 6.58; N, 6.69%

Example 105 Preparation of (±)-cis-7-(2-benzyloxycarbonyl-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1-cyano-2,3,5,6-dibenzobicyclo[2.2.2]octane (regioisomer 2)

The more polar regioisomer from the HPLC separation described in example 104 was designated regioisomer 2, the title compound, m.p. 104-7° found: C, 76.48; H, 6.65; N, 6.59. $C_{40}H_{41}N_3O_4$ requires C, 76.53; H, 6.58; N, 6.69%

Example 106 Preparation of cis-7-(1-S-methoxycarbonylethyl-aminocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

a. (±)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7-carboxylic acid

The material was prepared essentially as in example 14 but using neopentylamine hydrochloride as substrate instead of 1-adamantyl-amine.

b. cis-7-(1-S-methoxycarbonylethylaminocarbonyl)-8-(neopentyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The material was prepared essentially as in example 25 but using the compound prepared in step a. above instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid as substrate. found: C, 72.14; H, 7.32; N, 6.29. $C_{27}H_{32}N_2O_4$ requires C, 72.30; H, 7.19; N, 6.25%

Example 107 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. cis-7-(2-R-benzyloxycarbonylpyrrolidinocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers) The compound was prepared essentially as in example 46 but using the product of example 106 step a. as substrate instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid.

b. cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 48 but using the product of example 107 step a. as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt, m.p. 105-15° found: C, 57.98; H, 7.89; N, 6.07. $C_{35}H_{49}N_3O_9$. 4.0 H_2O requires C, 57.75; H, 7.89; N, 5.77%

Example 108 Preparation of 7-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7,8-ene

a. 7-carboxy-2,3,5,6-dibenzobicyclo[2.2.2]oct-7,8-ene

7-(methoxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7,8-ene (prepared as in J.C.S. Perkin I, 1984, 779) (0.5 g, 1.9 mmol) was dissolved in ethanol (20 ml) and sodium hydroxide (0.5 g) was added along with water (2 ml). The solution was stirred and refluxed for 1.5 h. The hot solution was poured onto 2M HCl (50 ml). The white precipitate formed was filtered off, washed with water and dried at 50° in vacuo. This compound was used without further purification.

b. 7-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]oct-7,8-ene

The acid prepared in step a. above (248 mg, 1 mmol) was dissolved in dry dichloromethane (10 ml) and diisopropylamine (0.52 g, 3

mmol) and PyBOP (0.52 g, 1 mmol) were added. After stirring at room temperatur for 5 min, 1-adamantylmethylamine (180 mg) was added. After stirring for a further 30 min whereupon the reaction mixture was evaporated. The residue was taken up in ethyl acetate and washed successively with 5% aqueous potassium hydrogensulphate solution (2 x 20 ml), saturated sodium hydrogencarbonate solution (20 ml), brine (20 ml), dried, filtered and evaporated to leave a crude product which was recrystallised from toluene. The white solid was dried in vacuo, m.p. 254-5° found: C, 81.28; H, 7.81; N, 3.40. $C_{28}H_{29}NO.\ H_2O$ requires C, 81.32; H, 7.50; N, 3.39%

Example 109 Preparation of (±)-7-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

a. (±)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

7-(methoxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (prepared as in US patent 5,055,468) (20 g, 80 mmol) was dissolved in methanol (220 ml) and potassium hydroxide (40 g) was added along with water (40 ml). The solution was stirred and refluxed for 4h. The solution was cooled, filtered through charcoal and treated with concentrated HCl. The buff precipitate formed was filtered off, washed with water and recrystallised from hot benzene. This compound was used without further purification.

b. (± 7-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

(±)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid (prepared in step a. above) (1.0 g) was heated with thionyl chloride (5 ml) and DMF (2 drops) at reflux for 30 min. On cooling and evaporation the pale yellow acid chloride was isolated.

The acid chloride (267 mg, 1.0 mmol) was dissolved in dry dichloromethane (5 ml) and and added with stirring to a solution of 1-adamantanemethylamine (182 mg, 1.1 mmol) and triethylamine (0.3 ml). After 30 min the solution was washe successively with

2M HCl and brine, dried, filtered and evaporated to leave a solid which was recrystallised from toluene (253 mg), m.p. 220-1° found: C, 84.88; H, 7.81; N, 3.39. $C_{28}H_{31}NO$ requires C, 84.81; H, 7.63; N, 3.39%

Example 110 Preparation of (±)-7-(1-adamantylmethoxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The material was prepared essentially as in example 109 except that 1-adamantanemethanol was used instead of 1-adamantanemethylamine in step b, m.p. 152-3° found: C, 84.42; H, 7.65. $C_{28}H_{30}O_2$ requires C, 84.38; H, 7.59%

Example 111 Preparation of cis-7-(1-S-methoxycarbonylethyl-aminocarbonyl)-8-(1-adamantylmethoxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The material was prepared essentially as in example 25 but using the compound prepared in example 13 instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid as substrate, m.p. 75-7° found: C, 74.27; H, 7.36; N, 2.80. $C_{33}H_{37}NO_5$. 0.06 mol DCM requires C, 74.53; H, 7.02; N, 2.62%

Example 112 Preparation of cis-7-(1-R-methoxycarbonylethyl-aminocarbonyl)-8-(1-adamantylmethoxycarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The material was prepared essentially as in example 111 but using D-alanine methyl ester hydrochloride instead of L-alanine methyl ester hydrochloride as substrate, m.p. 85-7° found: C, 74.38; H, 7.29; N, 2.75. $C_{33}H_{37}NO_5$. 0.05 mol DCM requires C, 74.63; H, 7.03; N, 2.63%

Example 113 Preparation of (±)-cis-7-(2-benzyloxycarbonylethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-dimethyl-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 29 but using (±)-cis-8-(1-adamantylmethylaminocarbonyl)-1,4-dimethyl-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7-carboxylic acid. This in turn was made by reaction of 1-adamantanemethylamine with 1,4-dimethyl-2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic acid anhydride essentially as in example 14. The anhydride was prepared by reaction of maleic anhydride with 9,10-dimethylanthracene in refluxing toluene. m.p. 170-3° found: C, 77.89; H, 7.49; N, 4.49. $C_{41}H_{46}N_2O_4$ requires C, 78.06; H, 7.49; N, 4.44%

Example 114 Preparation of (±)-cis-7-(1-S-methoxycarbonylethyl-aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1-nitro-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 25 but using (±)-cis-8-(1-adamantylmethylaminocarbonyl)-1-nitro-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane-7-carboxylic acid . This in turn was made by reaction of 1-adamantanemethylamine with 1-nitro-2,3,5,6-dibenzobicyclo-[2.2.2]octane-7,8-dicarboxylic acid anhydride essentially as in example 14. The anhydride was prepared by reaction of maleic anhydride with 9-nitroanthracene in refluxing toluene. The final mixture of diastereomers was separated into three components by HPLC (silica gradient elution of 5% ethyl acetate and 95% dichloromethane to 15% ethyl acetate and 85% dichloromethane). The least polar fraction was designated diastereomer 1. Found: C, 68.99; H, 6.78; N, 7.24. $C_{33}H_{37}N_3O_6$ requires C, 69.33; H, 6.52; N, 7.35%

Example 115 Preparation of (±)-cis-7-(1-S-methoxycarbonylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1-nitro-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The second least polar fraction from the HPLC separation described in example 114 was designated diastereomer 2. Found: C, 69.43; H, 6.69; N, 7.37. $C_{33}H_{37}N_3O_6$ requires C, 69.33; H, 6.52; N, 7.35%

Example 116 Preparation of (±)-cis-7-(1-S-methoxycarbonylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1-nitro-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 3)

The most polar fraction from the HPLC separation described in example 114 was designated diastereomer 3,
found: C, 69.21; H, 6.80; N, 7.22. $C_{33}H_{37}N_3O_6$ requires C, 69.33; H, 6.52; N, 7.35%

Example 117 Preparation of cis-7-(1-S-methoxycarbonyl-2-(3-indolyl)ethylaminocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 54 but using the product of example 106 step a. as substrate instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid. Found: C, 73.81; H, 6.49; N, 7.23. $C_{35}H_{37}N_3O_4$. 0.25 H_2O requires C, 73.98; H, 6.65; N, 7.39%

Example 118 Preparation of cis-7-(1-S-carboxy-2-(3-indolyl)ethylaminocarbonyl)-8-(neopentylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 107 but using the benzyl ester of L-tryptophan as substrate in step a. as substrate instead of the benzyl ester of D-proline. The compound

was characterised and tested as the N-methyl-D-glucamine salt Found: C, 65.91; H, 7.01; N, 7.31. $C_{41}H_{52}N_4O_9$ requires C, 66.11; H, 7.04; N, 7.52% ,

Example 119 Preparation of cis-7-(2-R-(carboxymethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of D-prolylglycine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 61.52; H, 7.52; N, 6.81. $C_{43}H_{58}N_4O_{10}$. 2.6 H_20 requires C, 61.65; H, 7.60; N, 6.69%

Example 120 Preparation of cis-7-(2-R-(carboxymethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The benzyl ester intermediate isolated after example 119 step a. was separated into its constituent diastereomers by recrystallisation from ethyl acetate. The mother liquors on concentration gave a benzyl ester which on hydrogenolysis gave the diastereomer of this example. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.12; H, 7.40; N, 6.95. $C_{43}H_{58}N_4O_{10}$ requires C, 65.30; H, 7.39; N, 7.08%

Example 121 Preparation of cis-7-(2-R-(carboxymethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The crystalline material from the recrystallisation described in example 120 on hydrogenolysis gave the diastereomer of this example. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 61.54; H, 7.75; N, 6.34.

$C_{43}H_{58}N_4O_{10}$. 2.9 H_2O requires C, 61.29; H, 7.62; N, 6.64%

Example 122 Preparation of cis-7-(2-R-(carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of D-prolyl-beta-alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 63.14; H, 7.78; N, 6.60. $C_{44}H_{60}N_4O_{10}$. 1.9 H_2O requires C, 63.02; H, 7.66; N, 6.68%

Example 123 Preparation of cis-7-(2-R-(methoxycarbonylmethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 but using the compound of example 119 as substrate instead of the compound of example 62. Found: C, 69.77; H, 7.08; N, 6.58. $C_{37}H_{43}N_3O_5$. 1.4 H_2O requires C, 69.97; H, 7.27; N, 6.62%

Example 124 Preparation of cis-7-(2-R-(methoxycarbonylethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 but using the compound of example 122 as substrate instead of the compound of example 62. Found: C, 71.15; H, 7.40; N, 6.56. $C_{38}H_{45}N_3O_5$. H_2O requires C, 71.13; H, 7.38; N, 6.54%

Example 125 Preparation of cis-7-(1-S-(carboxyethylamino-

carbonyl)ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of L-alanyl-beta-alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 60.56; H, 7.74; N, 6.53. $C_{42}H_{58}N_4O_{10}$. 3.1 H_2O requires C, 60.40; H, 7.75; N, 6.71%

Example 126 Preparation of cis-7-(1-S-(methoxycarbonylethylaminocarbonyl)ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 but using the compound of example 125 as substrate instead of the compound of example 62. Found: C, 69.51; H, 7.39; N, 6.49. $C_{36}H_{43}N_3O_5$. 1.4 H_2O requires C, 69.35; H, 7.41; N, 6.73%

Example 127 Preparation of cis-7-(1-S-(methylaminocarbonyl)-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 25 but using the trifluoroacetate salt of N-methyl-L-alaninamide instead of L-alanine methyl ester hydrochloride. Found: C, 72.12; H, 7.37; N, 7.50. $C_{33}H_{39}N_3O_3$. 1.2 H_2O requires C, 72.37; H, 7.63; N, 7.67%

Example 128 Preparation of cis-7-(1-S-(methoxycarbonyl)-ethylaminocarbonyl)-8-(1-RS-(1-adamantyl)ethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers A)

a. 8-(1-(1-adamantyl)ethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid (mixture of diastereomers)

This compound was prepared essentially as in example 14 but using 1-RS-(1-adamantyl)ethylamine (prepared as described in EP 178668) as substrate instead of 1-adamantanemethylamine.

b. cis-7-(1-S-(methoxycarbonyl)ethylaminocarbonyl)-8-(1-RS-(1-adamantyl)ethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers A)

This was prepared essentially as in example 25 but using the product of step a. instead of the product of example 14. The mixture of four compounds thus produced was separated into two pairs by use of preparative MPLC (silica 35% ethyl acetate and 65% hexane). The least polar pair were designated as the product of this example. found: C, 74.26; H, 7.60; N, 4.86. $C_{34}H_{40}N_2O_4$. 0.5 H_2O requires C, 74.29; H, 7.52; N, 5.10%

Example 129 Preparation of cis-7-(1-S-(methoxycarbonyl)-ethylaminocarbonyl)-8-(1-RS-(1-adamantyl)ethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers B)

The most polar pair of compounds isolated after the MPLC procedure described in example 128 were designated mixture B, the compounds of this example. Found: C, 74.01; H, 7.69; N, 4.90. $C_{34}H_{40}N_2O_4$. 0.5 H_2O requires C, 74.29; H, 7.52; N, 5.10%

Example 130 Preparation of cis-7-(1-S-(ethylcarbonyl)-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound of example 75 (0.37 g, 0.74 mmol) was dissolved in THF under an atmosphere of argon and cooled to 0°. A 1M solution of ethyl magnesium bromide in THF (3 ml) was added and the solution stirred for a further 2h before being allowed to warm to room temperature for overnight stirring. The reaction was quenched with 2M hydrochloric acid and after evaporation the the product was dissolved in ethyl acetate and washed succesively with saturated

aqueous sodium hydrogencarbonate and with brine. The organic layer was dried, filtered and evaporated to leave the crude product which was purified by column chromatography (silica 90% dichloromethane and 10% ethyl acetate). Yield 0.19 g, 50%, m.p 105-8°. Found: C, 77.87; H, 7.61; N, 5.22. $C_{34}H_{40}N_2O_3$ requires C, 77.83; H, 7.68; N, 5.34%

Example 131 Preparation of (±)-7-(methoxycarbonylmethyl)-cis-7-carboxy-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

a. Diels-Alder adduct of the methyl ester of aconitic anhydride and anthracene

The methyl ester of aconitic anhydride (10.2 g, 60 mmol) was dissolved in dry dichloromenthane (200 ml) and anthracene (7.12 g, 40 mmol) was added followed by anhydrous aluminium chloride (9.0 g, 60 mmol). The solution was stirred at room temperature overnight and then poured onto a mixture of ice and hydrochloric acid. The organic layer was separated and dried, filtered and evaporated to leave an orange oil which was recrystallised from toluene after treatment with activated charcoal. The product, a buff solid, was dried in air (9.01 g) and used in the next step.

b. (±)-7-(methoxycarbonylmethyl)-cis-7-carboxy-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The material was prepared essentially as in example 14 but using the material prepared in step a. above instead of (±)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic anhydride. The compound was characterised and tested as the N-methyl-D-glucamine salt found: C, 65.72; H, 7.61; N, 3.83. $C_{30}H_{52}N_2O_{10}$ requires C, 66.08; H, 7.39; N, 3.95%

Example 132 Preparation of cis-7-(1-S-(methoxycarbonyl)-ethylaminocarbonyl)-8-(2-adamantylmethylaminocarbonyl)-2,3,5,6-

dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 25 but using the compound of example 39 instead of 8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid as substrate, m.p. 105-110°. Found: C, 74.13; H, 7.17; N, 4.85. $C_{33}H_{38}N_2O_4$ .0.5 H_2O requires C, 73.99; H, 7.33; N, 5.23%

Example 133 Preparation of cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(2-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

The benzyl ester of the compound was prepared essentially as in example 46 but using the compound of example 39 instead of 8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid as substrate. The hydrogenolysis was performed as described in example 48. m.p. 105-110°. The compound was further characterised and tested as its N-methyl-D-glucamine salt found: C, 64.86; H, 7.79; N, 5.19. $C_{41}H_{55}N_3O_4$ .1.6 H_2O requires C, 64.56; H, 7.69; N, 5.51%

Example 134 Preparation of 8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-ene-7-carboxylic acid

a. dimethyl-2,3,5,6,-dibenzobicyclo[2.2.2.]oct-7-ene-7,8-dicarboxylate

The Diels-Alder reaction between anthracene (10g, 0.06 mol) and dimethyl acetylenedicarboxylate (8.3 ml, 0.07 mol) was performed essentially as in step a. of example 1 with the exeption that the reactants were refluxed for 24 hours.

b. 2,3,5,6,-dibenzobicyclo[2.2.2.]oct-7-ene-7,8-dicarboxylic acid

To a solution of potassium hydroxide (1.05 g, 18.8 mmol) in water (30 ml) was added the solution of the product of step a. (2.0 g,

6.2 mmol) in dioxan (10 ml). The reaction mixture was heated to reflux for 20 mins, cooled to room temperature and diluted with 2N hydrochloric acid. The precipitated solid was filtered, washed with water and dried (1.42 g, 78%).

c. 2,3,5,6,-dibenzobicyclo[2.2.2.]oct-7-ene-7,8-dicarboxylic acid anhydride

A mixture of the product of step b (1.4 g, 4.8 mmol and acetic anhydride (36 ml) was heated at reflux for 45 mins. The solvent was evaporated and the residue was triturated with diethyl ether to afford white solid (0.73 g, 55%).

d. 8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]oct-7-ene-7-carboxylic acid

This was performed essentially as in example 14 using the product of step c above as substrate instead of 2,3,5,6-dibenzo-bicyclo[2.2.2]oct-7,8-dicarboxylic anhydride. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 67.79; H, 7.51; N, 4.33. $C_{36}H_{46}N_2O_8$ requires C, 68.12; H, 7.30; N, 4.41%

Example 135 Preparation of cis-7-(1-S-methoxycarbonyl-ethylamino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]oct-7-ene

This was performed essentially as in example 25 using the product of example 134 as substrate instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-carboxylic acid found: C, 75.45; H, 6.79; N, 5.26. $C_{33}H_{36}N_2O_4$ requires C, 75.55; H, 6.92; N, 5.34%

Example 136 Preparation of cis-7-(2-R-(carboxymethylamino-carbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-ene

This was performed essentially as in example 119 using the product of example 134 as substrate instead of 8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-carboxylic acid. The compound was tested as the N-methyl-D-glucamine salt.

Example 137 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-difluoro-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. Diels alder reaction

This was performed essentially as in step a. of example 1 using 9,10-difluoroanthracene (prepared as in J.Org.Chem., 1989, 54, 1018) as substrate instead of anthracene.

b. (±)-cis-8-(1-adamantylmethylaminocarbonyl)-1,4-difluoro-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

This was performed essentially as in example 14 using the product of step a. above as substrate instead of 2,3,5,6-dibenzobicyclo[2.2.2]oct-7,8-dicarboxylic anhydride

c. cis-7-(2-R-benzyloxycarbonylpyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-difluoro-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This was performed essentially as in example 46 using the product of step b above as substrate instead of (±)-cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-carboxylic acid

d. cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-difluoro-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This was performed essentially as in example 48 using the product of step c above as substrate instead of the product of example 46.

The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 57.48; H, 7.43; N, 5.28. $C_{41}H_{53}F_2N_3O_9.4.5H_2O$ requires C, 57.82; H, 7.35; N, 4.93%

Example 138 Preparation of cis-7-(2-R-carboxy-4-R-hydroxy-pyrrolidinocarbonyl)-8-(2-adamantylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. (±)-cis-8-(2-adamantylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

This was prepared essentially as in example 11 using 2-adamantamine as substrate instead of 1-adamantamine.

b. cis-7-(2-R-benzyloxycarbonyl-4-R-hydroxy-pyrrolidinocarbonyl)-8-(2-adamantylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This was performed essentially as in example 46 using the product of step a. above as substrate instead of cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]oct-7-carboxylic acid

c. 7-(2-R-carboxy-4-R-hydroxy-pyrrolidinocarbonyl)-8-(2-adamantylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This was performed essentially as in example 48 using the product of step b above as substrate instead of the product of example 46. The compound was characterised and tested as the N-methyl-D-glucamine salt. Found: C, 60.86; H, 7.40; N, 5.31. $C_{40}H_{53}N_3O_{10}.2.9H_2O$ requires C, 60.97; H, 7.52; N, 5.33%

Example 139 Preparation of cis-7-(2-S-carboxypiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using

the benzyl ester of L-pipecolinic acid in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.39; H, 7.97; N, 5.28. $C_{42}H_{57}N_3O_9$. $2.0H_2O$ requires C, 64.35; H, 7.84; N, 5.36%

Example 140 Preparation of cis-7-(4-carboxypiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of 4-carboxypiperidine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.29; H, 8.05; N, 5.14. $C_{42}H_{57}N_3O_9$. $2.0H_2O$ requires C, 64.35; H, 7.84; N, 5.36%

Example 141 Preparation of cis-7-(2-S-(carboxymethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of 2-S-carboxymethylpyrrolidine (prepared as in WO 92/00295) in step a. instead of the dibenzyl ester of aspartic acid, $[\alpha]^D = -22.0°$ (c= 1.0 in methanol). The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 61.76; H, 7.89; N, 5.31. $C_{42}H_{57}N_3O_9$. $3.7H_2O$ requires C, 61.91; H, 7.97; N, 5.16%

Example 142 Preparation of cis-7-(2-R-(carboxymethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of 2-R-carboxymethylpyrrolidine (prepared as in

WO 92/00295) in step a. instead of the dibenzyl ester of aspartic acid, $[\alpha]^D$= +18.0° (c= 1.0 in methanol). The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 59.01; H, 8.12; N, 5.49. $C_{42}H_{57}N_3O_9$. 5.9H_2O requires C, 59.07; H, 8.12; N, 4.92%

Example 143 Preparation of cis-7-(2-S-(methoxycarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 using the product of example 141 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane, $[\alpha]^D$= -21.0° (c=2.0 in CHCl3). Found: C, 75.80; H, 7.49; N, 4.62. $C_{36}H_{42}N_2O_4$. 0.3 H_2O requires C, 75.62; H, 7.50; N, 4.90%

Example 144 Preparation of cis-7-(2-R-(methoxycarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 using the product of example 142 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane, $[\alpha]^D$= +18.0° (c=2.0 in $CHCl_3$). Found: C, 76.48; H, 7.46; N, 5.05. $C_{36}H_{42}N_2O_4$ requires C, 76.30; H, 7.47; N, 4.94%

Example 145 Preparation of cis-7-(2R-(1S-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the benzyl ester of D-prolyl-L-alanine in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated

at the benzyl ester stage by column chromatography (silica 60% dichloromethane and 40% ethyl acetate). The compound with the higher R_f was converted to the title compound by hydrogenation. The compound was tested as the N-methyl-D-glucamine salt.

Example 146 Preparation of cis-7-(2R-(1S-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 145 but using the compound with lower R_f after diastereomer separation in the final hydrogenation step. The compound was tested as the N-methyl-D-glucamine salt.

Example 147 Preparation of cis-7-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the benzyl ester of D-prolyl-D-alanine in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated at the benzyl ester stage by column chromatography (silica 60% dichloromethane and 40% ethyl acetate). The compound with the higher R_f was converted to the title compound by hydrogenation. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 59.62; H, 8.06; N, 6.23. $C_{44}H_{60}N_4O_{10}$ $4.7H_2O$ requires C, 59.45; H, 7.86; N, 6.30%

Example 148 Preparation of cis-7-(2R-(1R-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 147 but using the compound with lower R_f after diastereomer separation in the final hydrogenation step. The compound was tested as the N-methyl-D-glucamine salt.

Example 149 Preparation of cis-7-(2R-carboxy-4-S-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester of trans hydroxy-D-proline in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.63; H, 7.48; N, 5.38. $C_{41}H_{55}N_3O_{10}$ requires C, 65.67; H, 7.39; N, 5.38%

Example 150 Preparation of cis-7-(3-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester of 3-carboxypyrrolidine (prepared as in WO 92/00295) in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.33; H, 7.67; N, 5.48. $C_{41}H_{55}N_3O_9$. 1.4 H_2O requires C, 65.27; H, 7.65; N, 5.57%

Example 151 Preparation of cis-7-(3-methoxycarbonyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 63 using the product of example 150 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane. Found: C, 75.83; H, 7.41; N, 5.08. $C_{35}H_{40}N_2O_4$ requires C, 76.06; H, 7.29; N, 5.07%

Example 152 Preparation of cis-7-(3-(+)-ethoxycarbonyl-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-

dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using (+)ethyl nipecotate (prepared as described in J. Neurochem., 1976, 26, 1029) in step a. instead of the dibenzyl ester of aspartic acid to give the title compound directly without the need for subsequent deprotection. Found: C, 76.69; H, 7.64; N, 4.81. $C_{37}H_{44}N_2O_4$ requires C, 76.52; H, 7.63; N, 4.82%

Example 153 Preparation of cis-7-(3-(-)-ethoxycarbonyl-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using (-)ethyl nipecotate in step a. instead of the dibenzyl ester of aspartic acid to give the title compound directly without the need for subsequent deprotection. Found: C, 76.29; H, 7.61; N, 4.68. $C_{37}H_{44}N_2O_4$ requires C, 76.52; H, 7.63; N, 4.82%

Example 154 Preparation of cis-7-(3-(+)-methoxycarbonyl-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

a. cis-7-(3-(+)-carboxy-piperidinocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (separated diastereomers)

The compound was prepared essentially as in example 64 but using (+)benzyl nipecotate (prepared by standard means from (+) ethyl nipecotate) in step a. instead of the dibenzyl ester of aspartic acid to give the carboxylic acid as a mixture of diastereomers. The two diastereomers were separated by chromatography (silica 90% dichloromethane and 10% ethyl acetate).

b. cis-7-(3-(+)-methoxycarbonyl-piperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

diastereomer 1

The compound was prepared essentially as in example 63 using the less polar (higher R_f material) isolated in step a. above as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane.

Example 155 Preparation of cis-7-(3-(+)-methoxycarbonylpiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 63 using the more polar (lower R_f material) isolated in step a. of example 154 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane.

Example 156 Preparation of cis-7-(3-(-)-methoxycarbonylpiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 154 but using (-) benzyl nipecotate as substrate in step a. rather than (+) benzyl nipecotate. As in that example the less polar material was converted to the title compound in step b.

Example 157 Preparation of cis-7-(3-(-)-methoxycarbonylpiperidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 63 using the more polar (lower R_f material) isolated in step a. of example 156 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-

bicyclo[2.2.2]octane.

Example 158 Preparation of cis-7-(2R-(1methyl-1-carboxy-cyclopropylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the benzyl ester of D-prolyl-cyclopropylalanine (prepared by standard means) in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated at the benzyl ester stage by column chromatography (silica 60% dichloromethane and 40% ethyl acetate). The compound with the higher R_f was converted to the title compound by hydrogenation, $[\alpha]^D$= +10.0° (c= 1.0 in methanol). The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 58.54; H, 7.44; N, 6.03. $C_{45}H_{60}N_4O_{10}$ $5.6H_2O$ requires C, 58.92; H, 7.81; N, 6.11%

Example 159 Preparation of cis-7-(2R-(1methyl-1-carboxy-cyclopropylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 158 but using the compound with lower R_f after diastereomer separation in the final hydrogenation step. The compound was tested as the N-methyl-D-glucamine salt.

Example 160 Preparation of cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzo-bicyclo[2.2.2]octane (mixture of isomers 1)

a. 2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane-7,8-dicarboxylic anhydride

This was performed essentially as described in example 1 step a. except that 2-fluoroanthracene was used as reactant instead of anthracene.

b. 8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane-7-carboxylic acid.

The reaction was performed essentially as described in example 14 but using the compound described in step a. above rather than 2,3,5,6-dibenzobicyclo[2.2.2]octane-7,8-dicarboxylic anhydride.

c. cis-7-(2-R-benzyloxycarbonylpyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane.

The reaction was performed essentially as in example 46 but using the compound prepared in step b above, rather than (±)cis-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid.

d. cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane (mixture of isomers 1)

The reaction was performed essentially as in example 48 but using the compound prepared in step c above, rather than cis-7-(2-R-benzyloxycarbonylpyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane. The material which by this stage was a mixture of eight compounds was separated by HPLC (C8 column 60% acetonitrile, 40% water and 0.1% acetic acid) into three components. The material with a retention time of 15 min was designated the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 65.22; H, 7.38; N, 5.42. $C_{41}H_{54}FN_3O_6$ requires C, 65.49; H, 7.24; N, 5.59%

Example 161 Preparation of cis-7-(2-R-carboxypyrrolidinocarbonyl)-

8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane (mixture of isomers 2)

The mixture from example 160 step d with a retention time of 16 min was designated the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 64.99; H, 7.29; N, 5.59. $C_{41}H_{54}FN_3O_9$ requires C, 65.49; H, 7.24; N, 5.59%

Example 162 Preparation of cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3-(2-fluorobenzo)-5,6-benzobicyclo[2.2.2]octane (mixture of isomers 3)

The mixture from example 160 step d with a retention time of 22 min was designated the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 65.29; H, 7.42; N, 5.65. $C_{41}H_{54}FN_3O_9$ requires C, 65.49; H, 7.24; N, 5.59%

Example 163 Preparation of cis-7-(2R-(1-carboxy-1-methylethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the benzyl ester of D-prolyl-alpha-aminobutyric acid in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated at the benzyl ester stage by recrystallisation from ethyl acetate and column chromatography (silica 50% hexane and 50% ethyl acetate). The compound with the lower R_f was converted to the title compound by hydrogenation. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.91; H, 7.65; N, 6.60. $C_{45}H_{62}N_4O_{10}$ requires C, 65.99; H, 7.63; N, 6.84%

Example 164 Preparation of cis-7-(2R-(1-carboxy-1-methyl-

ethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 147 but using the compound with higher R_f after diastereomer separation in the final hydrogenation step. The compound was tested as the N-methyl-D-glucamine salt.

Example 165 Preparation of cis-7-(2-R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-8-fluoro-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as described in example 160 but performing the reaction in step a. with anthracene and 2-fluoromaleic anhydride (prepared as in J.Am.Chem.Soc., 1959, 81, 2678) instead of the reagents stated. No attempt was made at separation of the diastereomers at any stage. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 65.59; H, 7.18; N, 5.61. $C_{41}H_{54}FN_3O_9$ requires C, 65.49; H, 7.24; N, 5.59%

Example 166 Preparation of cis-7-(-N-(carboxymethyl)-N-(methoxycarbonylmethyl)aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 25 but using methyl N-(carboxymethyl)glycine (prepared as in Tetrahedron, 1984, 40, 1151) as substrate instead of L-alanine methyl ester. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 64.21; H, 7.25; N, 5.22. $C_{41}H_{55}N_3O_{11}$ requires C, 64.30; H, 7.24; N, 5.49%

Example 167 Preparation of cis-7-(-N-(4-(2-oxo-N-(carboxymethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomers 1 and

2)

The reaction was performed essentially as in example 64 but using the benzyl ester of N-carboxymethyl-2-oxo-4-aminopyrrolidine (prepared as in Peptide Research 1991, 4, 171) in step a. instead of the dibenzyl ester of aspartic acid. The compound was separated at the end of step a. into two pairs of diastereoisomers by column chromatography the higher R_f components being hydrogenated at step b to give the title compounds of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 57.23; H, 7.41; N, 6.13. $C_{42}H_{56}N_4O_{10}$ $5.5H_2O$ requires C, 57.54; H, 7.71; N, 6.39%

Example 168 Preparation of cis-7-(-N-(4-(2-oxo-N-(carboxymethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomers 3 and 4)

The reaction was performed essentially as in example 167 except that the lower R_f components were used in the hydrogenation step b. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 56.07; H, 7.39; N, 6.56. $C_{42}H_{56}N_4O_{10}$ $6.5H_2O$ requires C, 56.46; H, 7.78; N, 6.27%

Example 169 Preparation of cis-7-(-N-(4-(2-oxo-N-(methoxycarbonylmethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomers 1 and 2)

The compound was prepared essentially as in example 63 using the compound of example 167 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane. Found: C, 66.83; H, 7.21; N, 6.15. $C_{36}H_{41}N_3O_5$. $1.7CH_3OH$ and 0.4 CH_2Cl_2 requires C, 66.89; H, 7.21; N, 6.15%

Example 170 Preparation of cis-7-(-N-(4-(2-oxo-N-(methoxycarbonylmethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomers 3 and 4)

The compound was prepared essentially as in example 63 using the compound of example 168 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane. Found: C, 64.05; H, 6.71; N, 5.82. $C_{36}H_{41}N_3O_5$. 1.0CH_3OH and 1.0 CH_2Cl_2 requires C, 64.04; H, 6.65; N, 5.90%

Example 171 Preparation of cis-7-(1S-(carboxymethylaminocarbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of L-phenylalanylglycine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.11; H, 7.62; N, 6.35. $C_{47}H_{60}N_4O_{10}$. 2.3H_2O requires C, 63.95; H, 7.38; N, 6.35%

Example 172 Preparation of cis-7-(1S-(1R-carboxyethylaminocarbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of L-phenylalanyl-D-alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was tested as the mono-N-methyl-D-glucamine salt.

Example 173 Preparation of cis-7-(1R-(carboxymethylaminocarbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-

2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of D-phenylalanylglycine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the mono-N-methyl-D-glucamine salt. Found: C, 62.18; H, 7.48; N, 5.74. $C_{47}H_{60}N_4O_{10}$. $4.0H_2O$ requires C, 61.86; H, 7.51; N, 6.14%

Example 174 Preparation of cis-7-(1S-(carboxymethylaminocarbonyl)-2-(3-indolyl)phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 64 but using the benzyl ester of L-tryptophanylglycine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the mono-N-methyl-D-glucamine salt. Found: C, 58.88; H, 7.07; N, 6.62. $C_{40}H_{61}N_5O_{10}$. $3.2H_2O$ and 1.0 CH_2Cl_2 requires C, 58.73; H, 6.84; N, 6.85%

Example 175 Preparation of cis-7-(2R-(1-S-carboxy-2-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the dibenzyl ester of D-prolyl-L-aspartic acid in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated at the benzyl ester stage by column chromatography (silica 60% dichloromethane and 40% ethyl acetate). The compound with the higher R_f was converted to the title compound by hydrogenation. Found: C, 64.46; H, 6.97; N, 5.30. $C_{38}H_{43}N_3O_7$. 3.0 H_2O requires C, 64.48; H, 6.97; N, 5.63% ^1H NMR

Example 176 Preparation of cis-7-(2R-(1-S-carboxy-2-

carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 175 but using the compound with lower R_f after diastereomer separation in the final hydrogenation step. Found: C, 69.21; H, 6.73; N, 5.93. $C_{38}H_{43}N_3O_7$. 0.5 H_2O requires C, 68.86; H, 6.69; N, 6.34%

Example 177 Preparation of (±)-cis-8-(6-undecylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 14 but using 6-undecylamine as substrate instead of 1-adamantylmethylamine. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.38; H, 8.53; N, 5.33. $C_{36}H_{54}N_2O_8$. 1.0H_2O requires C, 65.43; H, 8.54; N, 4.23%

Example 178 Preparation of cis-7-(-N-(3S-(2-oxo-N-(carboxymethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 64 but using the benzyl ester of N-carboxymethyl-2-oxo-3S-aminopyrrolidine (prepared as in J. Org. Chem. 1982, 47, 105) in step a. instead of the dibenzyl ester of aspartic acid. The compound was tested as the N-methyl-D-glucamine salt.

Example 179 Preparation of cis-7-(-N-(3R-(2-oxo-N-(carboxymethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 64 but using the benzyl ester of N-carboxymethyl-2-oxo-3R-aminopyrrolidine (prepared as in J. Org. Chem. 1982, 47, 105) in step a. instead of

the dibenzyl ester of aspartic acid. The compound was tested as the N-methyl-D-glucamine salt.

Example 180 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-2S-methyl-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 64 but using the benzyl ester of α-methyl-D-prolyl-glycine (prepared as in J. Am. Chem. Soc., 1983, 105, 5390) in step a. instead of the dibenzyl ester of aspartic acid. The compound was tested as the N-methyl-D-glucamine salt.

Example 181 Preparation of cis-7-(2R-(aminocarbonylmethylamino-carbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 64 but using D-prolyl-glycinamide in step a. instead of the dibenzyl ester of aspartic acid to give the title compound directly. Obviously there was no need for a hydrogenation step. Found: C, 67.41; H, 7.01; N, 8.54. $C_{36}H_{42}N_4O_4$. $2.4H_2O$ requires C, 67.79; H, 7.39; N, 8.78%

Example 182 Preparation of cis-7-(1R-(aminocarbonylmethylamino-carbonyl)-phenethylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 64 but using D-phenylalanyl-glycinamide in step a. instead of the dibenzyl ester of aspartic acid to give the title compound directly. Obviously there was no need for a hydrogenation step. Found: C, 71.76; H, 7.01; N, 8.09. $C_{40}H_{44}N_4O_4$. $1.5H_2O$ requires C, 71.51; H, 7.05; N, 8.33%

Example 183 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-4R-hydroxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound was prepared essentially as in example 64 but using the benzyl ester of cis-4-hydroxy-D-prolylglycine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 56.39; H, 7.65; N, 7.96. $C_{43}H_{58}N_4O_{11}$. $6.2H_2O$ and 1.6 CH_3CN requires C, 56.37; H, 7.70; N, 7.97%

Example 184 Preparation of cis-7-(2S-(1S-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. cis-7-(2S-(1S-benzyloxycarbonylethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound of example 141 (250 mg, 0.45 mmol) was dissolved in dichloromethane (30 ml) and L-alanine benzyl ester p-toluenesulphonate salt (160 mg, 0.45 mmol) was added followed by PyBOP (235 mg, 0.45 mmol) and Hunigs base (240 ml, 1.35 mmol). The mixture was stirred at room temperature for 42 h and then washed with 5% potassium hydrogensulphate solution (15 ml), sodium hydrogencarbonate solution (15 ml) and saturated brine (15 ml). The solution was then dried and the product purified by chromatography (silica and ethyl acetate) to yield a colourless solid.

b. cis-7-(2S-(1S-carboxyethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 48 but using the product of step a. as substrate instead of the product of example 46. The compound was tested as the N-methyl-D-glucamine

salt.

Example 185 Preparation of cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 184 but using D-alanine benzyl ester p-toluenesulphonate salt in step a. rather than L-alanine benzyl ester p-toluenesulphonate salt. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 59.20; H, 7.64; N, 6.11. $C_{45}H_{62}N_4O_{11}$. $4.9H_2O$ requires C, 59.54; H, 7.98; N, 6.17%

Example 186 Preparation of cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

a. cis-7-(2S-carboxymethylpyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound of example 141 was separated into its constituent diastereomers by recrystallisation from dichloromethane. The crystals isolated were the title compound. In addition the other diastereomer was isolated by concentration of the mother liquors.

b. cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

This was prepared in two steps as described in example 185 but using the product from step a. above rather than the compound of example 141 as the substrate in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 187 Preparation of cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

This was prepared essentially as in example 185 but using the dichloromethane soluble diastereomer described in example 186 step a. as substrate in step a. rather than the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 188 Preparation of cis-7-(2R-(methoxycarbonylmethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound of example 123 was separated into its constituent diastereomers by chromatography (silica 30% ethyl acetate and 70% dichloromethane). The less polar material was designated the compound of this example. Found: C, 64.59; H, 6.76; N, 5.94. $C_{37}H_{43}N_3O_5$.0.3 EtOAc and 1.1 CH_2Cl_2 requires C, 64.70; H, 6.58; N, 5.76%

Example 189 Preparation of cis-7-(2R-(methoxycarbonylmethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane.

The more polar material isolated in example 188 was designated the compound of this example. Found: C, 70.27; H, 7.70; N, 6.63. $C_{37}H_{43}N_3O_5$ requires C, 69.97; H, 7.27; N, 6.62%

Example 190 Preparation of cis-7-(2R-(carboxymethyl(N-methyl)-aminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using

the benzyl ester of D-prolyl-sarcosine in step a. instead of the dibenzyl ester of aspartic acid. The compound was tested as the N-methyl-D-glucamine salt.

Example 191 Preparation of cis-7-(-N-(3R-(2-oxo-N-(methoxycarbonylmethyl)pyrrolidine))aminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The reaction was performed essentially as in example 63 using the compound of example 179 as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane. The compound was tested as the N-methyl-D-glucamine salt.

Example 192 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-dimethyl-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 137 but using 9,10-dimethylanthracene as substrate in step a. instead of 9,10-difluoroanthracene. In addition the mixture of diastereomers isolated after step c was separated into its constituent isomers using chromatography (silica 10% ethyl acetate and 90% dichloromethane). The less polar material was taken through to the title compound. The compound was further characterised and tested as the N-methyl-D-glucamine salt found: C, 64.71; H, 7.88; N, 5.06. $C_{43}H_{59}N_3O_9$. $2.0H_2O$ requires C, 64.65; H, 7.96; N, 5.26%

Example 193 Preparation of cis-7-(2-R-carboxy-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-1,4-dimethyl-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The more polar compound described in example 192 was hydrogenated to give the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found:

C, 61.67; H, 7.88; N, 4.82. $C_{43}H_{59}N_3O_9$. $4.0H_2O$ requires C, 61.88; H, 8.10; N, 5.04

Example 194 Preparation of cis-7-(2S-(carboxymethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 184 but using the benzyl ester of glycine in step a. rather than L-alanine benzyl ester p-toluenesulphonate salt. The compound was further characterised and tested as the N-methyl-D-glucamine salt, HPLC; R_T=16.2 mins, C8 column, CH_3CN 50%, H_2O 50%, 0.1% CH_3COOH.

Example 195 Preparation of cis-7-(2R-(1R-(2,2-dimethyl-1,3-dioxolane-4-methoxycarbonyl)-ethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound of example 147 (305 mg, 0.5 mmol) was dissolved in dry dichloromethane (3 ml) and solketal (66 ml, 0.5 mmol) was added. DMAP (2 mg) and DCCI (103 mg, 0.5 mmol) were added and the reaction mixture stirred at room temperature for 1h. After filtration the solution was evaporated to leave a foam which was purified by column chromatography (silica 95% dichloromethane and 5% methanol) to leave the title compound (195 mg). Found: C, 71.42; H, 7.45; N, 5.84. $C_{43}H_{53}N_3O_7$ requires C, 71.35; H, 7.38; N, 5.81%

Example 196 Preparation of cis-7-(2R-(1R-(pivaloyloxymethoxycarbonyl)-ethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

The compound of example 147 (305 mg, 0.5 mmol) was dissolved in DMF (2 ml) and pivaloyloxymethyl chloride (72 ml, 0.55 mmol) and caesium carbonate (82 mg, 0.5 mmol) was added. After gentle warming

the reaction was stirred at room temperature for 1h. The reaction mixture was poured onto brine (30 ml) and extracted with ethyl acetate (30 ml). The organic layer was washed with brine (2 x 30 ml) dried and evaporated. The material was completely purified by passage through a silica pad eluting with a 1:1 mixture of dichloromethane and ethyl acetate to leave the title compound (160 mg). Found: C, 71.21; H, 7.48; N, 5.62. $C_{43}H_{53}N_3O_7$ requires C, 71.35; H, 7.38; N, 5.81%

Example 197 Preparation of cis-7-(2R-aminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 25 but using D-prolinamide instead of the methyl ester of l-alanine.

Example 198 Preparation of cis-7-(2R-(carboxymethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

a. cis-7-(2R-carboxymethylpyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (separation of diastereomers)

The compound of example 142 was treated with dichloromethane. The dichloromethane insoluble material was designated diastereomer 1 and the soluble isomer designated diastereomer 2.

b. cis-7-(2R-(carboxymethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 194 except that the diastereomer 1 from step a. above was used as substrate instead of the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 199 Preparation of cis-7-(2R-(carboxymethylamino-carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 194 except that the diastereomer 2 from example 198 step a. was used as substrate instead of the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 200 Preparation of cis-7-(2R-(1S-carboxyethylamino-carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 184 except that the diastereomer 1 from example 198 step a. was used as substrate instead of the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 201 Preparation of cis-7-(2R-(1S-carboxyethylamino-carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 184 except that the diastereomer 2 from example 198 step a. was used as substrate instead of the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 202 Preparation of cis-7-(2R-(1R-carboxyethylamino-carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 185 except that the diastereomer 1 from example 198 step a. was used as substrate instead of the compound of example 141. The compound was tested

as the N-methyl-D-glucamine salt.

Example 203 Preparation of cis-7-(2R-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 185 except that the diastereomer 2 from example 198 step a. was used as substrate instead of the compound of example 141. The compound was tested as the N-methyl-D-glucamine salt.

Example 204 Preparation of cis-7-(2R-(carboxyethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester of trans-3-(2R-pyrrolidino)-but-2-enoic acid (prepared from benzyl(triphenylphosphoranylidene)acetate and N-(t-butoxycarbonyl)-D-prolinal by Wittig reaction) in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.81; H, 7.94; N, 5.14. $C_{43}H_{59}N_3O_6$. 2.0H_2O requires C, 64.77; H, 7.96; N, 5.27%

Example 205 Preparation of cis-7-(2S-(methoxycarbonylethenyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 25 but using the methyl ester of trans-3-(2S-pyrrolidino)-but-2-enoic acid (prepared from methyl(triphenylphosphoranylidene)acetate and N-(t-butoxycarbonyl)-L-prolinal by Wittig reaction) instead of L-alanine methyl ester. Found: C, 76.66; H, 7.39; N, 4.73. $C_{37}H_{42}N_2O_4$ requires C, 76.79; H, 7.32; N, 4.84%

Example 206 Preparation of cis-7-(2S-(methoxycarbonylethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

This was prepared by treating the compound of example 205 with 10% palladium on charcoal in an atmosphere of hydrogen gas. Found: C, 76.73; H, 7.79; N, 4.91. $C_{37}H_{44}N_2O_4$ requires C, 76.52; H, 7.64; N, 4.82%

Example 207 Preparation of cis-7-(1S-(aminocarbonylmethylaminocarbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The reaction was performed essentially as in example 25 but using L-phenylalanylglycinamide as substrate instead of L-alanine methyl ester. The mixture of diastereomers produced by this reaction was separated by column chromatography (silica and ethyl acetate). The less polar material was designated the title compound of this example. Found: C, 72.24; H, 7.02; N, 8.21. $C_{40}H_{44}N_4O_4.1.2\ H_2O$ requires C, 74.50; H, 6.87; N, 8.68%

Example 208 Preparation of cis-7-(1S-(aminocarbonylmethylaminocarbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The more polar material isolated from the separation in example 207 was designated the compound of this example. Found: C, 72.12; H, 6.95; N, 8.39. $C_{40}H_{44}N_4O_4.1.2\ H_2O$ requires C, 74.50; H, 6.87; N, 8.68%

Example 209 Preparation of (±)-7-(1-adamantylmethylaminocarbonylmethyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

The compound was prepared essentially as in example 131 except that

itaconic anhydride was used as substrate instead of the methyl ester of aconitic anhydride in step a. The compound was further characterised and tested as the N-methyl-D-glucamine salt, m.p. 115-120° . Found: C, 68.06; H, 7.71; N, 4.37. $C_{37}H_{50}N_2O_8$ requires C, 68.29; H, 7.74; N, 4.30%

Example 210 Preparation of 7-(1S-methoxycarbonylethylaminocarbonyl)-7-(1-adamantylmethylaminocarbonylmethyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

The compound was prepared essentially as in example 25 except that the compound of example 209 was used as substrate instead of the compound of example 14. Found: C, 75.36; H, 7.56; N, 4.99. $C_{34}H_{40}N_2O_4$ requires C, 75.53; H, 7.46; N, 5.18%

Example 211 Preparation of 7-(2R-carboxypyrrolidinocarbonyl)-7-(1-adamantylmethylaminocarbonylmethyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

The compound was prepared essentially as in example 160 except that the compound of example 209 was used in step c as substrate instead of the compound of example 160 step b. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 67.24; H, 7.74; N, 5.81. $C_{42}H_{57}N_3O_9$ requires C, 67.45; H, 7.68; N, 5.62%

Example 212 Preparation of (±)-cis-7-(2-carboxycyclopentylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers 1)

The compound was prepared essentially as in example 64 but using the benzyl ester of cis 2-amino-cyclopentanoic acid in step a. instead of the dibenzyl ester of aspartic acid. The mixture of compounds after step a. was separated by column chromatography (silica 85% dichloromenthane 15% ethyl acetate) to give two pairs

of diastereomers. The less polar material was hydrogenated to give the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 65.12; H, 7.75; N, 5.42. $C_{42}H_{57}N_3O_9.1.5\ H_2O$ requires C, 65.1; H, 7.80; N, 5.42%

Example 213 Preparation of (±)-cis-7-(2-carboxycyclopentylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers 2)

The compound was prepared essentially as in example 212 except that the more polar material after separation was hydrogenated to give the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.88; H, 7.91; N, 5.28. $C_{42}H_{57}N_3O_9.1.7\ H_2O$ requires C, 64.8; H, 7.82; N, 5.40%

Example 214 Preparation of cis-7-(2R-(1R-methoxycarbonylethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (single diastereomer)

The compound was prepared essentially as in example 63 except that the compound of example 147 was used as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers). Found: C, 72.88; H, 7.51; N, 6.58. $C_{38}H_{45}N_3O_5$ requires C, 73.17; H, 7.27; N, 6.74%

Example 215 Preparation of cis-7-(2S-(carboxyethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester of trans-3-(2S-pyrrolidino)-but-2-enoic acid (prepared from benzyl(triphenylphosphoranylidene)acetate and N-(t-

butoxycarbonyl)-L-prolinal by Wittig reaction) in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 66.64; H, 8.02; N, 5.60. $C_{43}H_{59}N_3O_9.0.6\ H_2O$ requires C, 66.80; H, 7.85; N, 5.44%

Example 216 Preparation of cis-7-(1S-carboxy-(2-naphthyl)-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester L-3-(2-naphthyl)alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 70.15; H, 7.33; N, 5.05. $C_{49}H_{59}N_3O_6.0.3\ H_2O$ requires C, 70.05; H, 7.16; N, 5.00%

Example 217 Preparation of cis-7-(1S-carboxy-(1-naphthyl)-ethylaminocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester L-3-(1-naphthyl)alanine in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 69.94; H, 7.14; N, 5.23. $C_{49}H_{59}N_3O_6.0.3\ H_2O$ requires C, 70.05; H, 7.16; N, 5.00%

Example 218 Preparation of cis-7-(1R-(1R-carboxyethylamino-carbonyl)-2-phenylethylaminocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester D-phenylalanyl-D-alanine in step a. instead of the

dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 64.21; H, 7.63; N, 6.36. $C_{48}H_{62}N_4O_{10}.2.3\ H_2O$ requires C, 64.28; H, 7.63; N, 6.36%

Example 219 Preparation of cis-7-(3-S-carboxy-1,2,3,4-tetrahydroisoquinolinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester 1,2,3,4-tetrahydroisoquinoline-3-S-carboxylic acid in step a. instead of the dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 66.75; H, 7.37; N, 5.08. $C_{46}H_{57}N_3O_{90}.1.7\ H_2O$ requires C, 66.80; H, 7.37; N, 5.08%

Example 220 Preparation of 7-(2R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

a. (±)-8-(1-adamantylmethyl-N-(methyl)aminocarbonylmethyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane-7-carboxylic acid

This was prepared essentially as in example 14 except that N-methyl-1-adamantanemethylamine was used as substrate instead of 1-adamantanemethylamine.

b. 7-(2R-benzyloxycarbonylpyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

This was prepared essentially as in example 46 except that the product of step a. was used as substrate instead of the product of example 14.

c. 7-(2R-carboxypyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-

(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

This was prepared essentially as in example 48 except that the product of step b above was used as substrate instead of the product of example 46. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 63.54; H, 7.87; N, 5.32. $C_{42}H_{57}N_3O_9.2.3\ H_2O$ requires C, 63.91; H, 7.87; N, 5.32%

Example 221 Preparation of 7-(2R-(carboxymethylaminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

The compound was prepared essentially as in example 194 except that the compound of example 220 was used as substrate instead of the compound of example 141 in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 222 Preparation of 7-(2R-(1S-carboxyethylaminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

The compound was prepared essentially as in example 184 except that the compound of example 220 was used as substrate instead of the compound of example 141 in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 223 Preparation of 7-(2R-(1R-carboxyethylaminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereoisomers)

The compound was prepared essentially as in example 185 except that the compound of example 220 was used as substrate instead of the compound of example 141 in step a. The compound was tested as the

N-methyl-D-glucamine salt.

Example 224 Preparation of cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. cis-7-(2S-(carboxymethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 141 except that the compound of example 220 step a. was used instead of the compound of example 14.

b. cis-7-(2S-(1R-carboxyethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 185 except that the compound from step a. above was used as substrate instead of the compound of example 141 in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 225 Preparation of cis-7-(2S-(1S-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 184 except that the compound from example 224 step a. was used as substrate instead of the compound of example 141 in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 226 Preparation of cis-7-(2R-(1S-carboxyethylamino-

carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

a. cis-7-(2R-(carboxymethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo-[2.2.2]octane (mixture of diastereomers)

The reaction was performed essentially as in example 142 except that the compound of example 220 step a. was used instead of the compound of example 14.

b. cis-7-(2R-(1S-carboxyethylaminocarbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 184 except that the compound from step a. above was used as substrate instead of the compound of example 141 in step a. The compound was tested as the N-methyl-D-glucamine salt.

Example 227 Preparation of cis-7-(2S-(methoxycarbonylmethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 25 but using the methyl ester L-prolylglycine as substrate instead of L-alanine methyl ester. Found: C, 62.87; H, 7.47; N, 5.02. $C_{37}H_{43}N_3O_5$. 1.1 EtOAc and 4.5 H_2O requires C, 63.12; H, 7.78; N, 5.33%

Example 228 Preparation of cis-7-(2S-(1R-carboxyethylaminocarbonyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 64 but using the benzyl ester L-prolyl-D-alanine in step a. instead of the

dibenzyl ester of aspartic acid. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 60.11; H, 8.22; N, 6.22. $C_{44}H_{60}N_4O_{10}$ .4.4 H_2O requires C, 59.81; H, 7.84; N, 6.34%

Example 229 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-5-oxopyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the benzyl ester D-pyroglutamyl-glycine in step a. instead of the dibenzyl ester of aspartic acid. The product of step a. was separated into its constituent diastereomers by chromatography (silica 30% ethyl acetate and 70% dichloromethane). The less polar material was hydrogenated to give the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 54.22; H, 7.26; N, 5.54. $C_{43}H_{56}N_4O_{11}$ .8.0 H_2O requires C, 54.42; H, 7.60; N, 5.90%

Example 230 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-5-oxopyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 229 except that the more polar material isolated after the chromatography was hydrogenated to give the compound of this example. The compound was further characterised and tested as the N-methyl-D-glucamine salt. Found: C, 54.88; H, 7.20; N, 6.11. $C_{43}H_{56}N_4O_{11}$ .8.0 H_2O requires C, 54.42; H, 7.60; N, 5.90%

Example 231 Preparation of cis-7-(2R-(1R-carboxyethylamino-carbonylmethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethyl-N-(methyl)aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 185 except that the compound from example 226 step a. was used as substrate instead of the compound of example 141 in step a.

Example 232 Preparation of cis-7-(2S-(1R-(methoxycarbonyl)-ethylaminocarbonylmethyl)-pyrrolidinocarbonyl)-8-(1-adamantyl-methylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (single diastereomer)

The compound was prepared essentially as in example 63 except that the compound of example 186 was used as substrate instead of cis-7-(1-S-carboxyl-2-methylpropylaminocarbonyl)-8-(1-adamantylmethyl-aminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

Example 233 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-4-thiopyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

a. cis-7-(2R-(t-butoxycarboylmethylaminocarbonyl)-4-thio-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

This compound was prepared essentially as in example 25 except that 2R-(t-butoxycarbonylmethylaminocarbonyl)-4-thiopyrrolidine was used as substrate instead of L-alanine methyl ester.

b. cis-7-(2R-(carboxymethylaminocarbonyl)-4-thiopyrrolidino-carbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzo-bicyclo[2.2.2]octane

The compound of step a. above was treated with trifluoroacetic acid to give the title compound of this example.

Example 234 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-

4-oxothio-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

This was prepared from the compound of example 233 step a. by treatment with ozone followed by treatment with trifluoroacetic acid.

Example 235 Preparation of cis-7-(2R-(carboxymethylaminocarbonyl)-4-dioxothio-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane

This was prepared from the compound of example 233 step a. by treatment with the tetrabutylammonium salt of oxone followed by treatment with trifluoroacetic acid.

Example 236 Preparation of cis-7-(2R-(3,5-dicarboxyphenylaminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 1)

The compound was prepared essentially as in example 64 but using the dibenzyl ester of D-prolyl-5-aminoisophthalic acid in step a. instead of the dibenzyl ester of aspartic acid. The diastereomers were separated at the benzyl ester stage by column chromatography (silica, 92% dichloromethane and 8% ethyl acetate). The compound with the higher R_f was converted to the title compound by hydrogenation. The compound was further characterised and tested as the mono-N-methyl-D-glucamine salt, HPLC; R_T=17.4 mins, C8 column, CH_3CN 50%, H_2O 50%, 0.1% CH_3COOH.

Example 237 Preparation of cis-7-(2R-(3,5-dicarboxyphenylaminocarbonyl)-pyrrolidinocarbonyl)-8-(1-adamantylmethylaminocarbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (diastereomer 2)

The compound was prepared essentially as in example 237 but using

the compound with lower R_f after diastereomer separation in the final hydrogenation step. The compound was further characterised and tested as the mono-N-methyl-D-glucamine salt, HPLC; R_t=9.4 mins, C8 column, CH_3CN 60%, H_2O 40%, 0.1% CH_3COOH.

Example 238 Preparation of cis-7-(2S-(1-R-carboxyethylamino-carbonylethyl)pyrrolidinocarbonyl)-8-(1-adamantylmethylamino-carbonyl)-2,3,5,6-dibenzobicyclo[2.2.2]octane (mixture of diastereomers)

The compound was prepared essentially as in example 185 but using the product of example 215 instead of the compound of example 141. The compound was further characterised and tested as the N-methyl-D-glucamine salt, HPLC; R_t=21.7 mins, C8 column, CH_3CN 50%, H_2O 50%, 0.1% CH_3COOH.

The following ^1H NMR data were obtained for the compounds described in the Examples:

Ex.1a. (d^6-DMSO) δ 7.5 (2H, m), 7.3 (2H, m), 7.2 (4H, m), 4.8 (2H, s), 3.6 (2H,s).

Ex.1b. (d^6-DMSO) δ 11.6 (1H, br s), 7.9 (1H, t), 7.4-6.9 (13H, m), 4.5 (1H, s), 4.4 (1H, s), 3.1 (1H, d), 2.9 (2H, m), 2.8 (1H, d), 2.5 (2H, t), 1.6 (2H, m).

Ex.2 (d^6-DMSO) δ 11.6 (1H, br s), 10.8 (1H, s), 8.0 (1H, t), 7.6-6.8 (13H, m), 4.5 (1H, s), 4.3 (1H, d), 3.3-3.0 (3H, d), 2.2-2.4 (3H, m).

Ex.3 (d^6-DMSO) δ 8.4 (1H, br s), 8.4 (1H, t), 7.4-6.8 (13H, m), 4.4 (2H, d), 4.1 (2H, m), 3.2 (1H, d), 2.8 (1H, d).

Ex.4 (d^6-DMSO) δ 8.4 (1H, t), 8.0-6.9 (15H, m), 4.7 (1H, dd), 4.5 (1H, dd), 4.5 and 4.3 (2H, 2xs), 3.3 (1H, d), 2.8 (1H, d).

Ex.5 (d^6-DMSO) δ 8.5 (1H, t), 8.0-6.9 (15H, m), 4.5 (2H, d), 4.3 (2H, m), 3.2 (1H, d), 2.8 (1H, d).

Ex.6 (d^6-DMSO) δ 11.6 (1H, br s), 7.8 (1H, m), 7.4-6.9 (8H, m), 4.5 (1H, s), 4.4 (1H, s), 3.2-2.6 (4H, m), 2.2-0.9 (11H, m).

Ex.7 (d^6-DMSO) δ 11.6 (1H, br s), 7.8 (1H, m), 7.4-6.9 (8H, m), 4.5 (1H, s), 4.4 (1H, s), 3.2 (1H, dd), 3.0-2.8 (2H, m), 2.8 (1H, dd) 1.2 (8H, m), 0.9 (3H, t).

Ex.8 (d^6-DMSO) δ 11.6 (1H, br s), 7.8 (1H, t), 7.4-6.9 (8H, m), 4.5 (1H, d), 4.4 (1H, d), 3.1 (1H, dd), 3.0-2.8 (2H, m), 2.7 (1H, dd) 1.3 (12H, m), 0.9 (3H, t).

Ex.9 (d^6-DMSO) δ 11.6 (1H, br s), 7.8 (1H, t), 7.4-6.9 (8H, m), 4.5 (1H, d), 4.4 (1H, d), 3.1 (1H, dd), 2.8-2.6 (3H, m), 1.8-0.7 (11H, m).

Ex.10 (d^6-DMSO) δ 12.6 (1H, br s), 7.7 (1H, t), 7.4-6.9 (8H, m), 4.5 (1H, d), 4.4 (1H, d), 3.0 (1H, dd), 2.9 (2H, m), 2.8 (1H, dd), 1.3 (2H, m), 0.9 (9H, s).

Ex.11 (d^6-DMSO) δ 7.3 (3H, m), 7.2 (1H, m), 7.1 (5H, m), 4.5 (1H, d), 4.4 (1H, d), 3.1 (1H, dd), 2.7 (1H, dd), 1.9 (3H, s), 1.8 (6H, m), 1.6 (6H, m).

Ex.12 (d^6-DMSO) δ 7.6 (1H, t), 7.4-6.9 (8H, m), 4.5 (1H, d), 4.4 (1H, d), 3.0 (1H, dd), 2.9 (2H, m), 2.8 (1H, dd), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m), 1.1 (2H, t).

Ex.13 (d^6-DMSO) δ 12.2 (1H br s), 7.4-7.0 (8H, m), 4.6 (1H, dd), 3.4 (1H, d), 3.3 (1H, d), 3.1 (1H, d), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m).

Ex.14 (d^7-DMF) δ 7.7 (1H, t), 7.4 (3H, m), 7.2 (3H,m), 7.1 (2H, m), 4.7 (1H, d), 4.6 (1H, d), 3.5 (1H, dd), 3.0 (1H, dd), 2.9 (1H, dd), 2.7 (1H, dd), 2.0 (3H, s), 1.7 (6H, m), 1.5 (6H, s).

Ex.15 (d^6-DMSO) δ 7.9 (1H, t), 7.0-7.4 (8H, m), 6.6 (1H,t), 4.5 (2H, d), 3.8-3.5 (2H, 2xdd), 3.6 (3H, s), 3.2 (1H, d), 3.0 (1H, dd), 2.5 (1H, dd), 1.9 (3H, b s), 1.2-1.7 (12H, m).

Ex.16a (d^6DMSO) δ 8.0 (1H, m), 7.4-7.0 (13, m), 6.6 (1H, m), 5.1 (2H, s), 4.4 (2H, s), 3.8 (1H, dd), 3.6 (1H, dd), 3.1 (1H, m), 3.0 (1H, d), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, q), 1.3 (6H, d).

Ex.16b (d^6-DMSO) δ 7.8 (1H, m), 7.3-7.0 (8H, m), 6.6 (1H, m), 4.5 (2H, s), 3.7 (1H, dd), 3.4 (1H, m), 3.1 (1H, d), 2.9 (1H, d), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.17 ($CDCl_3$) δ 7.6 (1H, d), 7.1-7.4 (7H, m), 4.9 (1H, t), 4.6 (1H, d), 4.5 (1H, d), 3.6 (3H, s), 3.3 (1H, dd), 3.2 (1H, dd), 2.9 (1H, m), 2.6 (1H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.18a ($CDCl_3$) δ 7.6-7.1 (8H, m), 6.0 (1H, d), 5.9 (1H, d), 4.0 (1H, dd), 3.8 (1H, dd).

Ex.18b ($CDCl_3$) δ 7.8-6.9 (15H, m), 4.9 (2H, d), 4.6 (1H, d), 4.4 (1H, d), 4.0 (1H, dd),3.8 (1H, dd).

Ex.18c (d^6-DMSO) δ 9.0 (1H, bs), 7.9-7.0 (15H, m), 5.4 (1H, s), 4.6 (2H, d), 4.4 (1H, m), 4.3 (1H, m), 3.1 (1H, m), 2.9 (1H, m).

Ex.19 (d^6-DMSO) δ 8.9 (1H, bs), 7.4-6.8 (13H, m), 4.6 (2H, s), 4.3 (1H, dd), 4.1 (1H, dd), 3.5 (1H, m), 3.0 (1H, dd), 2.8 (1H, dd).

Ex.20a ($CDCl_3$) δ 7.6-7.1 (8H, m), 5.0 (1H, d), 4.9 (1H, d), 4.2 (1H, dd), 4.1 (1H, dd)

Ex.20b (d^6-DMSO) δ 8.2 (1H, bs), 7.9-6.9 (15H, m), 4.7 and 4.5 (2H, 2xs), 4.2 (1H, d), 4.1 (1H, d), 3.1 (2H, m).

Ex.21 (d^6-DMSO) δ 10.8 (1H, s), 8.0 (1H, bs), 7.5-6.8 (13H, m), 4.7 and 4.4 (2H, 2xs), 3.2-2.9 (6H, m).

Ex.22 (d^6-DMSO) δ 7.7 (1H, bs), 7.4-6.9 (8H, m), 4.7 and 4.4 (2H,

2xs), 3.1 (2H, m) , 2.7 (1H, dd), 2.3 (1H, d), 1.8 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.23 (d^6-DMSO) δ 8.0 (1H, t), 7.9 (1H, m), 7.4-7.0 (8H, m), 4.6 (2H, d), 3.9 (1H, m), 3.2 (1H, m), 3.1 (1H, m), 2.9 (1H, m), 2.5 (1H, m), 1.9 (3H, s), 1.6 (6H, q), 1.4 (6H, s), 1.2 (3H, dd).

Ex.24 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.2 (1H, t), 5.3 (1H, t), 4.5 (2H, s), 3.7 (3H, s), 3.3 (2H, m), 3.2 (2H, q), 2.7 (2H, ddd), 2.4 (2H, t), 1.9 (3H, s), 1.4 (6H, q), 1.2 (6H, s).

Ex.25 ($CDCl_3$) δ 7.5-7.1 (8H, m), 5.9 and 5.7 (1H, 2 x d), 5.3 and 5.1 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 3.7 (3H, s), 3.3-3.1 (2H, dd), 2.9-2.5 (2H, m), 1.9 (3H, s), 1.7 (6H, q), 1.3 (6H, d), 1.2 and 0.9 (3H, d).

Ex.26 ($CDCl_3$) δ 7.5-7.1 (8H, m), 5.7 (1H, d), 5.3 (1H, t), 4.6 (2H, m), 4.3 (1H, m), 3.7 (3H, s), 3.2 (2H, s), 2.8-2.6 (2H, dd), 1.9 (3H, s), 1.7 (6H, q), 1.3 (6H, d), 1.1 (3H, d).

Ex.27 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.1 (1H, t), 5.2 (1H, d), 4.6 (2H, m), 4.2 (1H, m), 3.7 (3H, s), 3.2 (2H, dd), 2.8-2.5 (2H, dd), 1.9 (3H, s), 1.6 (6H, q), 1.3 (6H, d), 0.9 (3H, d).

Ex.28 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.1 and 5.9 (1H, 2 x d), 5.4 and 5.2 (1H, 2 x t), 4.6 (2H, d), 4.3 (1H, m), 3.7 (3H, s), 3.2 (2H, ddd), 2.9-2.5 (2H, m), 2.0 (3H, s), 1.7 (6H, q), 1.3 (6H, d), 1.2 (3H, d).

Ex.29 ($CDCl_3$) δ 7.5-7.1 (13H, m), 5.8 (1H, t), 5.2 (2H, s), 5.1(1H, t) 4.6 (2H, d), 3.3 (2H, q), 3.3-3.0 (2H, q), 2.8-2.6 (2H, ddd), 2.4 (2H, q), 1.8 (3H, s), 1.7 (6H, q), 1.3 (6H, d).

Ex.30 ($CDCl_3$) δ 7.6 (2H, d), 7.3-7.1 (7H, m), 4.8(1H, t) 4.6 (1H, d), 4.5 (1H, d), 3.5 (1H, m), 3.3 (1H, d), 3.1 (2H, m), 2.9 (1H, q), 2.4 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.31 (d^6-DMSO) δ 7.5-6.8 (12H, m), 4.5 (2H, m), 4.0 (1H, m),

3.3-2.5 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 and 1.3 (6H, 2 x s), 1.1 and 1.0 (3H, 2 x d).

Ex.32 (d^6-DMSO) δ 7.3 (4H, m), 7.1 (4H, m), 6.9-6.6 (2H, m), 4.5 and 4.3 (1H, 2 x t), 4.5 (2H, m), 3.6 (1H, m), 3.2 (1H, m), 3.0-2.8 (3H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m), 0.9 and 0.8 (3H, 2 x d).

Ex.33 ($CDCl_3$) δ 7.4-7.1 (13H, m), 5.7 (1H, d), 5.3 (1H, t), 5.1 (2H, s), 4.6 (1H, s), 4.5 (1H, s), 4.3 (1H, m), 3.2 (2H, s), 2.8 (1H, dd), 2.6 (1H, dd), 1.9 (3H, s), 1.6 (6H, q), 1.3 (6H, d), 1.1 (3H, d).

Ex.34 ($CDCl_3$) δ 7.5-7.1 (13H, m), 6.0 (1H, d), 5.1 (3H, m), 4.6 (2H, m), 4.4 (1H, m), 3.3 (1H, dd), 3.2 (1H, dd) 2.9 (1H, dd), 2.5 (1H, dd), 2.0 (3H, s), 1.7 (6H, q), 1.3 (9H, m).

Ex.35 (d^6-DMSO) δ 7.5 (1H, d), 7.4-7.2 (4H, m), 7.0 (4H, m), 6.8 (1H, t), 4.5 (2H, s), 4.0 (1H, m), 3.0 (2H, m), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, m), 1.1 (3H, d).

Ex.36 (d^6-DMSO) δ 7.7 (1H, d), 7.3 (2H, m), 7.2 (2H, m), 7.1 (2H, m), 7.0 (2H, m), 6.6 (1H, t), 4.5 (2H, s), 4.0 (1H, m), 3.0 (1H, d), 2.9 (1H, d), 2.6 (2H, m), 1.9 (3H, s), 1.6 (6H, q), 1.3 (6H, m), 1.1 (3H, d).

Ex.37b (d^6-DMSO) δ 7.6 (1H, t), 7.3 (2H, m), 7.0 (4H, m), 4.8 (1H, d), 4.6 (1H, d), 3.7 (6H, 2 x s), 3.1 (1H, dd), 2.7-2.4 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.4 (6H, m).

Ex.38 (d^6-DMSO) δ 7.4 (1H, t), 7.3 (2H, m), 7.0 (2H, m), 6.6 (2H, m), 4.8 (1H, d), 4.7 (1H, d), 3.7 (6H, 2 x s), 3.1 (1H, dd), 2.7-2.4 (3H, m), 1.9 (3H, s), 1.6 (6H, q), 1.4 (6H, m).

Ex.39 (d^6-DMSO) δ 11.6 (1H, bs), 7.8 (1H, t), 7.3 (3H, m), 7.0 (5H, m), 4.5 (1H, d), 4.4 (1H, d), 3.1 (2H, m), 2.9 (1H, m), 2.7 (1H, dd), 2.0-1.4 (15H, m).

Ex.40 (d^6-DMSO) δ 7.7 and 7.5 (1H, 2 x d), 7.4-7.0 (8H, m), 6.8 and 6.7 (1H, 2 x t), 4.5 (1H, m), 4.4 (2H, s), 3.0-2.7 (8H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, 2 x s), 1.1 and 1.0 (3H, 2 x d).

Ex.41 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.0 and 5.7 (1H, 2 x d), 5.4 and 5.0 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 3.7 (3H, s), 3.3-3.1 (2H, m), 3.0-2.6 (2H, m), 1.6-1.4 (5H, m), 1.2-1.1 (7H, m),0.7 (2H, m).

Ex.42 ($CDCl_3$) δ 7.6 (1H, m), 7.3-7.0 (7H, m), 4.6 (3H, m), 4.3 (1H, m), 3.7 (3H, s), 3.5-3.3 (3H, m), 3.0 and 2.8 (3H, 2 x s), 2.8 (1H, m), 2.3 (1H, m), 1.9 (3H, s), 1.6 (6H, q), 1.1 (6H, d).

Ex.43 ($CDCl_3$) δ 7.6 (1H, m), 7.3-7.0 (7H, m), 4.6 (3H, m), 4.3 (1H, m), 4.2 (2H, m), 3.5-3.3 (3H, m), 3.0 and 2.8 (3H, 2 x s), 2.8 (1H, m), 2.4 (1H, m), 1.9 (3H, s), 1.6 (6H, q), 1.3 (3H, m), 1.1 (6H, d).

Ex.44a (d^6-DMSO) δ 12.7 (1H, s), 7.4-7.1 (8H, m) 4.8 (2H, m), 4.0 (2H, m) 3.2 (1H, dd), 3.15 (1H, dd), 1.43 (3H, t).

Ex.44b (d^6-DMSO) δ 8.1 (1H, t), 7.4-7.0 (8H, m), 4.7 (1H, d), 4.65 (1H, d), 4.0 (2H, m), 3.4 (1H, dd), 3.1 (1H, dd), 2.9 (1H, dd), 2.6 (1H, dd),1.9-1.4 (15H, m), 1.1 (3H, t).

Ex.44c (d^6-DMSO) δ 15-13 (1H, br s), 7.5-7.0 (9H, m), 4.8 (2H, s), 3.2 (2H, s), 2.7 (2H, s), 1.7-0.9 (15H, m).

Ex.45 ($CDCl_3$) δ 7.3 (4H, m), 7.1 (4H, m), 4.6 (2H, m), 3.5 (3H, s), 3.4-3.6 (2H, m), 3.2 (1H, 2 x s), 2.0 (3H, br s), 1.7 (6H, q), 1.4 (6H, d).

Ex.46 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (13H, m), 5.4-5.0 (2H, m), 4.9-4.4 (3H, m), 3.7-3.1 (4H, m), 3.0-2.2 (2H, m), 2.2-1.8 (7H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.47 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (13H, m), 5.4-5.0 (2H, m),

4.9-4.4 (3H, m), 3.7-3.1 (4H, m), 3.0-2.2 (2H, m), 2.2-1.8 (7H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.48 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (7H, m), 5.3 (1H, br s), 4.7-4.2 (3H, m), 3.8-3.2 (5H, m), 3.1 and 2.8 (1H, m) 2.3 (2H, m), 2.0 (5H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.49 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (7H, m), 5.3 (1H, br s), 4.7-4.2 (3H, m), 3.8-3.2 (5H, m), 3.1 and 2.8 (1H, m) 2.3 (2H, m), 2.0 (5H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.50 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (7H, m), 4.7-4.3 (4H, m), 3.8-3.2 (7H, m), 3.0 and 2.8 (1H, m), 2.4-1.8 (8H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.51 ($CDCl_3$) δ 7.6 (1H, m), 7.3 (7H, m), 4.7-4.3 (4H, m), 3.8-3.2 (7H, m), 3.0 and 2.8 (1H, m), 2.4-1.8 (8H, m), 1.6 (6H, q), 1.2 (6H, m).

Ex.52 (d6-DMSO) δ 10.8 (1H, s), 7.5 (1H, d), 7.3 (6H, m), 7.0 (7H, m), 6.5 (1H, m), 4.5 (1H, m), 4.4 (1H, m), 3.1 (2H, s), 3.0 (1H, dd), 2.9 (1H, dd), 2.7 (2H, m), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.3 (6H, d).

Ex.53 (d6-DMSO) δ 10.9 (1H, 2 x s), 7.9 and 7.6 (1H, 2 x d), 7.5-7.2 (6H, m), 7.1 (7H, m), 6.6 (1H, m), 4.5 (2H, m), 4.3 (1H, m), 3.5 (3H, s), 3.0 (4H, dd), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.54 (d^6-DMSO) δ 10.9 (1H, 2 x s), 7.9 and 7.6 (1H, 2 x d), 7.5-7.2 (6H, m), 7.1 (7H, m), 6.6 (1H, m), 4.5 (2H, m), 4.3 (1H, m), 3.5 (3H, s), 3.0 (4H, dd), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.55a (diastereomer 1, higher R_f) (d^6-DMSO) δ 10.9 (1H, s), 7.5-6.9 (19H, m), 6.7 (1H, m), 4.9 (2H, m), 4.5 (2H, m), 4.3 (1H, m), 3.0 (4H, m), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.55a (diastereomer 2, lower R_f) (d^6-DMSO) δ 10.8 (1H, s), 7.9 (1H, d), 7.4-6.9 (18H, m), 6.6 (1H, m), 5.0 (2H, m), 4.5 (1H, s), 4.42 (1H, s), 4.38 (1H, m), 3.1-2.9 (4H, m), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, d).

Ex.55b (d^6-DMSO) δ 10.9 (1H, s), 7.5 (2H, m), 7.4-6.9 (12H, m), 6.6 (1H, t), 4.4 (2H, m), 4.2 (1H, s), 3.0 (4H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, q), 1.2 (6H, m).

Ex.56 (d^6-DMSO) δ 10.8 (1H, s), 7.8 (1H, d), 7.4-6.9 (13H, m), 6.5 (1H, t), 4.5 (1H, s), 4.4 (1H, s), 4.3 (1H, m), 3.1 (1H, m), 3.0 (1H, dd), 2.9 (2H, m), 2.4 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, m).

Ex.57 (d^6-DMSO) δ 10.9 (1H, s), 7.6 (2H, m), 7.4-6.9 (12H, m), 6.6 (1H, t), 4.4 (2H, m), 4.2 (1H, s), 3.0 (4H, m), 2.5 (2H, m), 1.8 (3H, s), 1.6 (6H, q), 1.2 (6H, m).

Ex.58 ($CDCl_3$) δ 8.1 (1H, s), 7.6 (1H, d), 7.4-6.9 (11H, m), 6.6 (1H, m), 6.5 (1H, m), 5.5 (1H, m), 4.8 (1H, m), 4.4 (1H, s), 4.2 (1H, m), 3.2 (4H, m), 2.7 (1H, m), 2.3 (1H, m), 2.0 (3H, s), 1.6 (6H, q), 1.2 (6H, m).

Ex.59 (d^6-DMSO) δ 8.6 (1H,t) 8.1 (1H,t), 7.3-7.0 (9H,m), 6.4 (1H,d), 6.2 (1H,d), 4.6 (2H,dd), 4.2 (2H,m), 3.2 (2H,d), 2.9(1H,m), 2.5 (1H,m), 1.9 (3H,s), 1.6 (6H,q), 1.4 (6H,d).

Ex.60 ($CDCl_3$) δ 7.7 (1H,d), 7.4 (1H,d), 7.3-7.0 (9H,m), 4.9 (1H,s), 4.7 (1H,d), 4.6 (1H,t), 3.9 (3H,m), 3.3 (2H,s), 2.6 (1H,q), 2.2 (1H,q), 1.7 (3H,s), 1.5(6H,q), 0.9 (6H,s).

Ex.61 ($CDCl_3$) δ 7.6-7.0 (13H, m), 6.1 and 5.8 (1H 2xd), 5.5 and 5.3 (1H, 2xt), 5.1 (2H, m), 4.6-4.2 (3H, m), 3.3-3.1 (2H, m), 2.9 (1H, m), 2.6 (1H, m), 1.9 (4H, s), 1.6 (6H, m), 1.3 (6H, m), 0.8-0.6 (6H, m).

Ex.62 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.9 and 6.5 (1H 2xm), 5.5 and 5.4 (1H, 2xm), 4.5 (2H, m), 4.3 and 4.2 (1H, m), 3.3 (2H, m), 3.0-2.4

(2H, m), 2.0 (4H, s), 1.6 (6H, m), 1.3 (6H, m), 0.8 (6H, m).

Ex.63 ($CDCl_3$) δ 7.5-7.2 (8H, m), 5.9 and 5.7 (1H 2xd), 5.3 and 5.2 (1H, m), 4.6(2H, bt), 4.2 (1H, m), 3.7 (3H, d), 3.3 (2H, m), 2.9 and 2.6 (2H, m), 1.9 (4H, s), 1.6 (6H, m), 1.3 (6H, m), 0.98-0.76 (6H, m).

Ex.64b (d^6-DMSO) δ 12.4 (1H, br s), 7.8-6.8 (11H, m), 4.4 (2H, m), 4.2 (1H, m), 3.0 (2H, m), 2.6-2.3 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.65 (d^6-DMSO) δ 12.6 (1H, br s), 7.9-6.9 (14H, m), 6.6 and 6.5 (1H, 2xt), 4.5 (2H, m), 4.4 (1H, m), 3.0 (2H, m), 2.8-2.3 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.66 (d^6-DMSO) δ 7.3-7.0 (10H, m), 4.5 (1H, s), 4.4 (1H, s), 3.6 (3H, s), 3.0 (2H, m), 2.7 (1H, m), 2.5 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m), 1.1 (6H, 2 x s).

Ex.67 (d^6-DMSO) δ 7.4-7.0 (10H, m), 4.5 (1H, s), 4.4 (1H, s), 3.1 (1H, m), 2.9 (1H, m), 2.7 (1H, m), 2.5 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m), 1.1 (6H, 2 x s).

Ex.68 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (7H, m), 5.8 (1H, br s), 4.9-4.3 (5H, m), 3.7- 3.1 (4H, m), 2.9-2.1 (4H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.69 ($CDCl_3$) δ 7.6 (1H, d), 7.4-7.1 (8H, m), 4.7 (1H, t), 4.6 (1H, d), 4.5 (1H, d), 4.4 (2H, m), 3.8 (1H, m), 3.6 (1H, d), 3.4 (1H, dd), 3.2 (1H, d), 2.8 (1H, dd), 2.4 (2H, m), 2.2 (1H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.70 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (7H, m), 5.8 (1H, br s), 4.9-4.3 (5H, m), 3.7- 3.1 (4H, m), 2.9-2.1 (4H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.71 ($CDCl_3$) δ 7.6 (1H, d), 7.4-7.1 (8H, m), 4.7 (1H, d), 4.6 (1H, d), 4.4 (3H, m), 3.8 (3H, s), 3.7 (1H, m), 3.6-3.2 (4H,m), 2.8

(1H, dd), 2.4 (1H, dd), 2.1 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.72 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (8H, m), 4.8-4.4 (5H, m), 3.9-3.1 (8H, m), 2.9-2.1 (3H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.73 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (8H, m), 4.8-4.4 (4H, m), 3.9-3.7 (3H, m), 3.3-2.6 (3H, m), 2.5-2.1 (3H, m), 2.0 (3H, s), 1.6 (8H, m), 1.1 (6H, m).

Ex.74 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (8H, m), 4.8-4.2 (4H, m), 3.9-2.1 (12H, m), 2.0 (3H, s), 1.6 (8H, m), 1.1 (6H, m).

Ex.75 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.2 and 6.1 (1H, 2 x d), 5.4 and 5.3 (1H, 2 x t), 4.5 (3H, s), 3.3-3.1 (2H, m), 2.7 (2H, m), 1.9 (3H, s), 1.7 (6H, m), 1.3 (9H, m).

Ex.76 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.2 and 5.9 (1H, 2 x d), 5.4 and 5.2 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 3.2 (2H, m), 2.9-2.4 (2H, m), 2.1 (3H, s), 1.9 (3H, s), 1.7 (6H, m), 1.3 (9H, m).

Ex.77 ($CDCl_3$) δ 7.5-7.0 (8H, m), 6.2 and 5.8 (1H, 2 x d), 5.4 and 5.1 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 4.1 (2H, m), 3.5-3.2 (2H, m), 2.8 (1H, m), 2.6 (1H, m), 1.9 (3H, s), 1.7 (8H, m), 1.2 (9H, m), 0.9 (3H, m)

Ex.78 ($CDCl_3$) δ 7.6 (1H, d), 7.4-7.1 (8H, m), 4.6-4.2 (3H, m), 3.6-3.2 (5H, m), 2.8 (1H, dd), 2.4 (2H, m), 2.0 (5H, m), 1.6 (6H, m), 1.3 (6H, m).

Ex.79 ($CDCl_3$) δ 7.6-7.1 (8H, m), 5.4 (1H, br s), 4.86-4.4 (3H, m), 3.7-2.8 (6H, m), 2.4 (2H, m), 2.0 (5H, m), 1.6 (6H, m), 1.3 (6H, m).

Ex.80 ($CDCl_3$) δ 7.6 (1H, d), 7.4-7.1 (7H, m), 4.6-4.3 (4H, m), 3.8 (3H, s), 3.5 (3H, m), 3.2 (1H, dd), 2.8 (1H, dd), 2.4 (1H, dd), 2.0 (7H, m), 1.6 (6H, m), 1.2 (6H, s).

Ex.81 ($CDCl_3$) δ 7.6-7.1 (8H, m), 4.8-4.4 (4H, m), 3.7 and 3.6 (3H, 2 x s), 3.5-2.9 (5H, m), 2.4-1.8 (8H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.82 (d^6-DMSO) δ 7.6-6.9 (8H, m), 4.5 (2H, m), 4.1 (1H, m), 3.7-3.3 (2H, m), 3.1 (2H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.83 (d^6-DMSO) δ 7.7-6.9 (8H, m), 4.5 (2H, m), 4.1 (1H, m), 3.6-3.3 (2H, m), 3.1 (2H, m), 2.6 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.84 ($CDCl_3$) δ 7.6 (1H, d), 7.3-7.1 (7H, m), 6.6 (1H, d), 5.9 (1H, t), 4.6 (1H, d), 4.4 (2H, m), 3.8 (3H, s), 3.7 (2H, m), 3.6 (1H, m) 3.2 (1H, dd), 3.0 (1H, dd), 2.9 (1H, dd), 2.7 (1H, dd), 2.0 (3H, s), 1.7 (6H, m), 1.4 (6H, m).

Ex.85 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.5 (1H, d), 5.6 (1H, t), 4.5 (2H, 2 x s), 4.4 (1H, m), 3.7 (6H, m), 3.3 (1H, dd), 3.2 (1H, dd), 2.9 (1H, dd), 2.5 (1H, dd), 2.0 (3H, s), 1.7 (6H, m), 1.3 (6H, m).

Ex.86 ($CDCl_3$) δ 7.7-7.1 (8H, m), 6.4 (1H, s), 5.8 (1H, s), 5.3 (1H, s), 5.0 (1H, t), 4.6 (1H, d), 4.5 (1H, d), 3.8 (3H, s), 3.4 (1H, dd), 3.2 (1H, dd), 2.7 (1H, dd), 2.5 (1H, dd), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, s).

Ex.87 (d^6-DMSO) δ 8.0-6.9 (9H, m), 4.9 and 4.8 (1H, 2 x m), 4.6-4.3 (3H, m), 3.5-2.7 (7H, m), 2.5-2.2 (2H, m), 1.8 (3H, s), 1.5 (6H, m), 1.1 (6H, m).

Ex.88 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (8H, m), 5.5-5.2 (1H, m), 4.6-4.4 (3H, m), 3.7- 3.2 (3H, m), 3.1-2.6 (2H, m), 2.3 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (5H, m), 1.2 (6H, m).

Ex.89 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (7H, m), 5.3-4.3 (4H, m), 3.8-2.6 (8H, m), 2.3 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (5H, m), 1.2 (6H, m).

Ex.90 (d^6-DMSO) δ 8.1-6.9 (9H, m), 4.9-4.1 (5H, m), 3.7-3.1 (7H,

m), 2.9-2.1 (4H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.91 (d^6-DMSO) δ 8.1-6.9 (9H, m), 4.9-4.1 (5H, m), 3.8-3.1 (7H, m), 2.9-2.1 (4H, m), 2.0 (3H, s), 1.6 (6H, m), 1.1 (6H, m).

Ex.92 (d^6-DMSO) δ 7.5-7.0 (13H, m), 6.4 (1H, d), 5.2 (1H, t), 4.5 (3H, m), 3.7 (3H, s), 3.6 (2H, s), 3.2 (2H, dd), 2.6 (4H, m), 2.0 (3H, s), 1.6 (6H, m), 1.2 (6H, s).

Ex.93 ($CDCl_3$) δ 7.4-6.9 (13H, m), 6.3 (1H, d), 5.2 (1H, t), 4.5 (3H, m), 3.6 (3H, s), 3.5 (2H, s), 3.1 (2H, dd), 2.6 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, s).

Ex.94 (d^6-DMSO) δ 7.3 (3H, m), 7.1 (6H, m), 4.9-4.5 (3H, m), 3.3 (1H, m), 3.0 (1H, m), 2.8-2.5 (5H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m), 1.1 (3H, m).

Ex.95 (d^6-DMSO) δ 7.3 (3H, m), 7.1-6.9 (6H, m), 4.9-4.5 (3H, m), 3.3 (1H, m), 3.0 (1H, m), 2.8-2.5 (5H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m), 1.1 (3H, m).

Ex.96 (d^6-DMSO) δ 7.4 (3H, m), 7.1 (5H, m), 5.0-4.4 (3H, m), 3.6 and 3.5 (3H, 2 x s), 3.2 (1H, m), 3.0 (1H, m), 2.8 and 2.7 (3H, 2 x s), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m), 1.2-0.9 (3H, m).

Ex.97 (d^6-DMSO) δ 7.4 (3H, m), 7.1-6.9 (5H, m), 5.0-4.3 (3H, m), 3.6 and 3.5 (3H, 2 x s), 3.3 (1H, m), 3.0 (1H, m), 2.8-2.5 (5H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3-1.0 (9H, m).

Ex.98 ($CDCl_3$) δ 7.7 (1H, d), 7.4-7.1 (7H, m), 4.6 (2H, m), 4.5 (1H, t), 3.5 (1H, m), 3.4 (2H, m), 3.3 (2H, m), 3.1 (1H, m), 2.7 (1H, q), 2.4 (1H, q), 1.9 (3H, s), 1.9-1.8 (4H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.99 (d^6-DMSO) δ 7.4-7.0 (9H, m), 6.4 (1H, t), 4.4 (2H, m), 3.3 (1H, d), 3.1 (1H, dd), 2.9 (1H, dd), 2.5 (1H, q), 2.4 (3H, d), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.100 ($CDCl_3$) δ 7.7 (1H, d), 7.4-7.1 (7H, m), 4.6 (2H, m), 4.4 (1H, t), 3.5 (1H, d), 3.1 (1H, dd), 2.9 (6H, 2 x s), 2.7 (1H, dd), 2.5 (1H, dd), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.101 ($CDCl_3$) δ 7.4 (2H, m), 7.3-7.1 (6H, m), 5.9 (1H, m), 5.7 (1H, m), 4.5 (2H, m), 3.2 (2H, d), 3.0 (2H, m), 2.6 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m), 0.9 (3H, t).

Ex.102 ($CDCl_3$) δ 7.5-7.1 (8H, m), 5.9 (1H, t), 5.3 (1H, d), 4.5 (2H, d), 3.7 (2H, m), 3.1 (2H, s), 2.8 (1H, m), 2.6 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.2 (6H, m), 0.8 (6H, d).

Ex.103 (d^6-DMSO) δ 7.4-7.0 (8H, m), 6.7 (1H, m), 6.6 (2H, m), 4.5 (2H, d), 3.0 (1H, d), 2.9 (1H, d), 2.6 (1H, m), 2.5 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.104 ($CDCl_3$) δ 7.7 (1H, m), 7.6 (1H, m), 7.4 (1H, m), 7.4-7.2 (10H, m), 6.0 (1H, t), 5.3 (1H, t), 5.1 (2H, s), 4.5 (1H, d), 3.4 (1H, m), 3.3 (2H, dt), 3.1 (1H, dd), 2.8 (1H, dd), 2.7 (1H, dd), 2.4 (2H, t), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.105 ($CDCl_3$) δ 7.8 (1H, m), 7.7 (1H, m), 7.4 (1H, m), 7.4-7.2 (10H, m), 6.3 (1H, t), 5.2 (1H, t), 5.1 (2H, s), 4.6 (1H, d), 3.4 (1H, m), 3.3 (2H, dd), 3.2 (1H, d), 2.8 (1H, dd), 2.7 (1H, dd), 2.4 (2H, t), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.106 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.3-6.0 (1H, 2 x d), 5.6 and 5.3 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 3.7 (3H, m), 3.3 (2H, m), 2.9 (1H, m), 2.7 (1H, m), 1.2 (3H, dd), 0.8 (9H, d).

Ex.107 (d^6-DMSO) δ 8.0-6.9 (9H, m), 4.5-3.9 (3H, m), 3.5-2.6 (6H, m), 2.2-1.6 (4H, m), 0.8 (9H, d).

Ex.108 ($CDCl_3$) δ 7.4 (4H, m), 7.0 (4H, m), 5.7 (2H, d), 5.2 (1H, d), 3.0 (2H, d), 2.0 (3H, s), 1.7 (6H, q), 1.5 (6H, s).

Ex.109 ($CDCl_3$) δ 7.4-7.1 (8H, m), 5.0 (1H, t), 4.6 (1H, d), 4.4 (1H, d), 2.8 (3H, m), 2.2 (1H, m), 1.9 (4H, m), 1.6 (6H, m), 1.3

(6H, s).

Ex.110 ($CDCl_3$) δ 7.4-7.0 (8H, m), 4.7 (1H, d), 4.4 (1H, t), 3.6 (2H, dd), 3.0 (1H, m), 2.2 (1H, m), 2.1 (1H, m), 2.0 (3H, s), 1.7 (6H, m), 1.5 (6H, q).

Ex.111 ($CDCl_3$) δ 7.5-7.1 (8H, m), 5.6 (1H, t), 4.6 (1H, s), 4.5 (1H, dd), 4.3 (1H, m), 3.7 (3H, 2 x s), 3.6 (1H, t), 3.4-3.1 (3H, m), 1.9 (3H, m), 1.7 (6H, q), 1.4 (6H, s), 1.2 (3H, dd).

Ex.112 ($CDCl_3$) δ 7.5-7.1 (8H, m), 5.6 (1H, t), 4.6 (1H, s), 4.5 (1H, dd), 4.3 (1H, m), 3.8 (3H, 2 x s), 3.6 (1H, t), 3.4-3.1 (3H, m), 1.9 (3H, m), 1.7 (6H, q), 1.4 (6H, s), 1.2 (3H, dd)

Ex.113 (d^6-DMSO) δ 7.4 (5H, m), 7.3 (4H, m), 7.1 (4H, m), 5.1 (2H, q), 3.1 (2H, m), 2.8 (2H, q), 2.4 (2H, m), 1.8 (3H, s), 1.6 (6H, m), 1.2 (6H, s).

Ex.114 (d^6-DMSO) δ 7.7-6.8 (10H, m), 4.6 (1H, s), 4.1 (1H, m), 3.6 (4H, m), 3.4 (1H, m), 2.7 (1H, q), 2.3 (1H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, s), 1.2 (3H, d).

Ex.115 (d^6-DMSO) δ 8.1-6.8 (10H, m), 4.6 (1H, s), 4.0 (1H, m), 3.6 (4H, m), 3.4 (1H, m), 2.7 (1H, q), 2.3 (1H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3 (6H, s), 1.2 (3H, m).

Ex.116 (d^6-DMSO) δ 8.0-6.8 (10H, m), 4.5 (1H, s), 4.0 (1H, m), 3.6 (4H, m), 3.4 (1H, m), 2.6 (1H, q), 2.3 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, s), 1.0 (3H, d).

Ex.117 ($CDCl_3$) δ 8.6 and 8.2 (1H, 2 x s), 7.5-7.1 (13H, m), 6.3 and 6.0 (1H, 2 x d), 5.4 and 5.2 (1H, 2 x t), 4.8-4.4 (3H, m), 3.6 (3H, s), 3.3-2.3 (6H, m), 0.8 (9H, 2 x s).

Ex.118 ($CDCl_3$) δ 8.2-6.4 (15H, m), 5.6 and 5.4 (1H, 2 x t), 4.8-4.2 (3H, m), 3.3-2.5 (6H, m), 0.8 (9H, 2 x s).

Ex.119 ($CDCl_3$) δ 7.6-7.0 (10H, m), 6.4 (1H, m) 5.0 (1H, m), 4.6-

4.4(2H, m), 4.3-4.0 (2H, m), 3.9-3.2 (3H, m), 2.9-2.6 (2H, m), 2.3 (1H, m), 2.1-1.9 (7H, m), 1.6 (6H, m), 1.4 and 1.2 (6H, 2 x s).

Ex.120 ($CDCl_3$) δ 7.6-7.0 (10H, m), 6.1 (1H, m), 5.0-4.4 (3H, m), 4.2 (2H, m), 3.9-3.2 (3H, m), 2.9-2.6 (2H, m), 2.1-1.9 (8H, m), 1.6 (6H, m), 1.2 (6H, s).

Ex.121 ($CDCl_3$) δ 7.6-7.0 (10H, m), 6.1 (1H, s), 4.8-4.4 (3H, m), 4.2-3.3 (5H, m), 2.9 (2H, m), 2.3 (1H, m), 2.1-1.9 (7H, m), 1.6 (6H, m), 1.2 (6H, s).

Ex.122 ($CDCl_3$) δ 7.6-7.1 (10H, m), 6.0 (1H, m), 4.8-4.3 (3H, m), 3.8-3.2 (7H, m), 2.9 (1H, m), 2.6 (2H, m), 2.1-1.9 (7H, m), 1.6 (6H, m), 1.2 (6H, s).

Ex.123 ($CDCl_3$) δ 7.6-7.1 (9H, m), 6.0 (1H, m), 4.6-4.0 (5H, m), 3.9-3.2 (6H, m), 2.9-2.3 (3H, m), 2.1-1.9 (7H, m), 1.6 (6H, m), 1.4 and 1.2 (6H, 2 x s).

Ex.124 ($CDCl_3$) δ 7.6-7.1 (9H, m), 5.9 (1H, m), 4.6-4.2 (3H, m), 3.8-3.1 (8H, m), 3.0-2.2 (5H, m), 2.1-1.9 (7H, m), 1.6 (6H, m), 1.4 and 1.2 (6H, 2 x s).

Ex.125 (d^6-DMSO) δ 7.7-7.5 (2H, m), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.0 (1H, m), 3.8-3.2 (4H, m), 2.8-2.6 (2H, m), 2.3 (2H, m), 1.9 (3H, m), 1.6 (6H, m), 1.3 (6H, 2 x s), 1.1 (3H, 2 x d).

Ex.126 ($CDCl_3$) δ 7.4-6.9 (9H, m), 5.9 (1H, m), 5.6 (1H, m), 4.5 (2H, m), 4.2 (1H, m), 3.7 (3H, s), 3.4 (4H, m), 2.8 (2H, m), 2.5 (2H, m), 2.0 (3H, s), 1.7 (6H, m), 1.3 (6H, 2 x s), 1.1 (3H, 2 x d).

Ex.127 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.8 (1H, m), 6.1 and 5.9 (2H, m), 4.5 (2H, m), 4.3 (1H, m), 3.2 (2H, s), 2.9-2.5 (5H, m), 2.0 (3H, s), 1.6 (6H, m), 1.3 (9H, m).

Ex.128b ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.0 and 5.4 and 5.3 and 5.2 (2H, 4 x d), 4.6 (2H, m), 4.3 (1H, m), 3.7 (3H, 2 x s), 3.5 (1H,

m), 3.2 (2H, m), 2.0 (3H, s), 1.6-0.9 (15H, m), 0.8 (3H, 2 x d).

Ex.129 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.2 and 6.0 and 5.3 and 5.2 (2H, 4 x d), 4.6 (2H, m), 4.4 (1H, m), 3.7 (3H, 2 x s), 3.5 (1H, m), 3.2 (2H, m), 2.0 (3H, m), 1.8-0.9 (15H, m), 0.8 (3H, 2 x d).

Ex.130 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.2 and 6.0 (1H, 2 x d), 5.4 and 5.2 (1H, 2 x t), 4.6 (2H, m), 4.3 (1H, m), 3.3-3.1 (2H, m), 2.9-2.3 (4H, m), 2.0 (3H, s), 1.6 (6H, m),1.3 (6H, 2 x s), 1.1 (6H, m).

Ex.131b (d^6-DMSO) δ 7.6-6.9 (9H, m), 4.6 (1H, s), 4.3 (1H, s), 3.6 (3H, s), 3.5 (1H, m), 2.9-2.5 (4H, m), 2.0 (3H, s), 1.6 (6H, m),1.3 (6H, s).

Ex.132 (d^6-DMSO) δ 7.9 and 7.5 (1H, 2 x d), 7.4-6.9 (9H, m), 4.4 (2H, m), 4.2-4.0 (1H, m), 3.6 (3H, 2 x s), 3.0 (4H, m), 2.0 (3H, s), 1.6 (6H, m),1.3 (6H, 2 x s), 1.2 (3H, m).

Ex.133 ($CDCl_3$) δ 7.6-7.1 (9H, m), 5.3 (2H, m), 4.6-4.2 (3H, m), 3.6-3.1 (4H, m), 2.7 (1H, m), 2.1-1.2 (18H, m).

Ex.134d (d^6-DMSO) δ 13.5-12.5 (1H, br s), 8.3 (1H, t), 7.4-7.0 (8H, m), 5.7 (1H, s), 5.4 (1H, s), 2.8 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m).

Ex.135 (d^6-DMSO) δ 8.8 (1H, d), 8.1 (1H, t), 7.5-7.0 (8H, m), 5.59 (1H, s), 5.56 (1H, s), 4.4 (1H, m), 3.6 (3H, s), 2.9 (2H, d), 1.9 (3H, s), 1.6 (6H, m), 1.4 (6H, m), 1.3 (3H, d).

Ex.136 (d^6-DMSO) δ 12.6 (1H, br s),8.4 (1H, t), 8.1 (1H, t), 7.5-6.9 (8H, m), 5.8 (1H, s), 5.4 (1H, s), 4.4 (1H, m), 3.9-3.5 (2H, m), 3.3-2.5 (4H, m), 2.1-1.4 (13H, m), 1.3 (6H, m).

Ex.137d ($CDCl_3$) δ 7.8 (4H, m), 7.3 (4H, m), 6.1 and 5.5 (1H, br s), 4.6 and 4.33 (1H, dd), 3.9-2.3 (7H, m), 2.0 (6H, m), 1.7 (6H, m), 1.4 (6H, m).

Ex.138c ($CDCl_3$) δ 7.6-7.0 (8H, m), 5.9 and 5.0 (1H, 2xd), 4.6-4.3

(5H, m), 3.8-3.1 (4H, m), 2.4-1.9 (2H, m), 1.8-1.0 (15H, m).

Ex.139 ($CDCl_3$) δ 7.7-7.0 (8H, m), 4.6-4.3 (3H, m), 3.8-2.8 (7H, m), 2.3 (2H, m), 1.9-1.0 (19H, m).

Ex.140 ($CDCl_3$) δ 7.7-7.0 (8H, m), 4.6-4.0 (4H, m), 3.8-2.2 (8H, m), 1.9 (4H, m), 1.6 (9H, m), 1.0 (6H, m).

Ex.141 ($CDCl_3$) δ 7.6-7.0 (8H, m), 5.0-4.5 (3H, m), 4.3 and 4.2 (1H, 2xm), 3.6-3.0 (5H, m), 2.7 (1H, m), 2.4 (1H, m), 2.2 (1H, m), 1.8 (7H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.142 ($CDCl_3$) δ 7.6 (1H, m), 7.2 (7H, m), 5.0-4.6 (3H, m), 4.3 and 4.1 (1H, 2xm), 3.6-3.0 (5H, m), 2.9 (1H, m), 2.7 (1H, m), 2.4 (1H, m), 2.2 (1H, m), 1.9 (6H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.143 ($CDCl_3$) δ 7.6 (1H, m), 7.2 (7H, m), 4.6 (3H, m), 4.4 and 4.2 (1H, 2m), 3.65 and 3.6 (3H, 2s), 3.5-3.0 (5H, m), 2.7 (1H, m), 2.3 (1H, m), 2.1-1.4 (14H, m), 1.2 (6H, m).

Ex.144 ($CDCl_3$) δ 7.6-7.1 (8H, m), 4.8-4.5 (3H, m), 4.4 and 4.2 (1H, 2m), 3.6 (3H, m), 3.5-2.0 (7H, m), 2.0-1.4 (14H, m), 1.2 (6H, m).

Ex.145 ($CDCl_3$) δ 7.6-6.9 (8H, m), 5.5 (1H, m), 4.7 (1H, t), 4.5 (2H, m), 4.2 (1H, m), 3.7-3.2 (5H, m), 2.9 (1H, m), 2.7 (1H, m), 2.2-1.7 (7H, m), 1.5 (9H, m), 1.2 (6H, m).

Ex.146 ($CDCl_3$) δ 7.6-7.0 (8H, m), 6.3 (1H, m), 4.5 (2H, d), 4.3 (2H, m), 3.8-3.2 (5H, m), 2.9 (1H, m), 2.6 (1H, m), 2.0 (7H, m), 1.7 (6H, m), 1.4 (9H, m).

Ex.147 ($CDCl_3$) δ 7.6-7.0 (8H, m), 6.1 (1H, m), 4.8-4.2 (4H, m), 3.6-3.2 (5H, m), 2.9 (1H, m), 2.3 (1H, m), 2.2-1.8 (7H, m), 1.6 (9H, m), 1.2 (6H, m).

Ex.148 ($CDCl_3$) δ 7.8-7.0 (8H, m), 4.8-4.2 (5H, m), 3.7-3.3 (3H, m), 3.2 (1H, m), 2.7 (1H, d), 2.6 (1H, m), 2.4 (1H, m), 2.2-1.2

(13H, m), 1.1 (6H, m), 0.8 (3H, d).

Ex.149 (d^6-DMSO) δ 12.5 (1H, br s), 7.4-6.8 (9H, m), 5.1-4.1 (5H, m), 3.9 (1H, m), 3.7 (1H, m), 3.3-2.9 (4H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.150 (d^6-DMSO) δ 7.3 (3H,m), 7.1 (5H, m), 6.8-6.3 (1H, m), 4.5 (2H, s), 3.7-2.7 (7H, m), 2.5 (2H, m), 1.9 (5H, m), 1.6 (6H, m), 1.2 (6H, s).

Ex.151 ($CDCl_3$) δ 7.7-7.1 (8H, m), 4.6 (2H, br,s), 4.5 (1H, m), 3.7 (3H, m), 3.65-2.0 (9H, m), 1.9 (3H, br,s), 1.6 (7H, m), 1.3 (1H, m), 1.1 (6H, s).

Ex.152 ($CDCl_3$) δ 7.6 (1H, d), 7.2 (7H, m), 4.8-4.2 (3H, m), 4.1 (2H, m), 3.9-2.0 (9H, m), 1.9 (3H, s), 1.6 (10H, m), 1.2 (3H, m), 1.1 (6H, s).

Ex.153 ($CDCl_3$) δ 7.6 (1H, d), 7.2 (7H, m), 4.8-4.2 (3H, m), 4.1 (2H, m), 3.9-2.0 (9H, m), 1.9 (3H, s), 1.6 (10H, m), 1.2 (3H, m), 1.1 (6H, s).

Ex.154b ($CDCl_3$) δ 7.7 (1H, m), 7.2 (7H, m), 4.8-4.2 (3H, m), 3.8 (1H, m), 3.62 and 3.64 (3H, 2xs), 3.6-2.0 (8H, m), 1.9 (3H, s), 1.6 (8H, m), 1.2 (2H, m), 1.1 (6H, s).

Ex.155 ($CDCl_3$) δ 7.7 (1H, m), 7.2 (7H, m), 4.6-4.2 (3H, m), 3.8 (1H, m), 3.63 and 3.65 (3H, 2xs), 3.6-2.0 (8H, m), 1.9 (3H, s), 1.6 (10H, m), 1.1 (6H, s).

Ex.156 ($CDCl_3$) δ 7.7 (1H, m), 7.2 (7H, m), 4.8-4.2 (3H, m), 3.8 (1H, m), 3.63 and 3.65 (3H, 2xs), 3.6-2.0 (8H, m), 1.9 (3H, s), 1.6 (8H, m), 1.3 (2H, m), 1.1 (6H, s).

Ex.157 ($CDCl_3$) δ 7.6 (1H, d), 7.2 (7H, m), 4.8-4.3 (3H, m), 3.8 (1H, m), 3.63 and 3.65 (3H, 2xs), 3.6-2.0 (8H, m), 1.9 (3H, s), 1.6 (10H, m), 1.1 (6H, s).

Ex.158 (d^6-DMSO) δ 8.2 (1H, s), 7.3 (3H, m), 7.0 (5H, m), 6.7 (1H, t), 4.47 and 4.48 (2H, 2xs), 3.9 (1H, m), 3.5-2.9 (4H, m), 2.6 (1H, m), 2.4 (1H, m), 1.8 (4H, m), 1.6 (9H, m), 1.3 (8H, m), 1.0 (2H,s).

Ex.159 (d^6-DMSO) δ 8.3 (1H, t), 7.5 (1H, s), 7.3 (3H, m), 7.0 (5H, m), 4.50 and 4.52 (2H, 2xs), 4.1 (1H, t), 3.4 (2H, m), 3.1 (1H, m), 2.9 (1H, d), 2.7 (2H, m), 1.9 (4H, m), 1.6 (9H, m), 1.3 (6H, m), 1.2(1H, m), 0.9 (1H, m), 0.7 (2H,m).

Ex.160d ($CDCl_3$) δ 7.7 (1H, d), 7.4-7.1 (6H, m), 6.9 (1H, m), 5.0 (1H, d), 4.6 (1H, s), 4.3 (1H, m), 3.5 (3H, m), 3.3 (1H, m), 2.9 (1H, m), 2.5-1.4 (14H, m), 1.2 (6H, m).

Ex.161 ($CDCl_3$) δ 7.6 (1H, d), 7.4-7.0 (6H, m), 6.9 (1H, m), 5.0 (1H, s), 4.6 (2H, m), 4.3 (1H, m), 3.5 (3H, m), 3.2 (2H, m), 2.8-1.4 (13H, m), 1.2 (6H, m).

Ex.162 ($CDCl_3$) δ 7.7 (1H, d), 7.4-7.1 (6H, m), 6.9 (1H, m), 5.0 (1H, m), 4.6 (1H, m), 4.3 (1H, m), 3.5 (3H, m), 3.3 (1H, m), 2.9 (1H, m), 2.5-1.4 (14H, m), 1.2 (6H, m).

Ex.163 (d^6-DMSO) δ 8.2 (1H, t), 7.5 (1H, s), 7.3 (3H, m), 7.0 (5H, m), 4.5 (2H, d), 4.0 (1H, m), 3.1-3.4 (2H, m), 3.0 (1H, m), 2.9 (1H, d), 2.8-2.6 (2H, m), 1.9-1.3 (19H, m), 1.08 and 1.13 (6H, 2xs).

Ex.164 (d^6-DMSO) δ 7.9(1H, s), 7.3-6.8 (8H, m), 6.8 (1H, t), 4.5 (2H, s), 4.0 (1H, m), 3.1-3.4 (3H, m), 3.0 (1H, m), 2.85 (2H, m), 2.1 (1H, m), 2.0-1.0 (24H, m).

Ex.165 ($CDCl_3$) δ 7.7-6.9 (8H, m), 5.7 (1H, m), 5.4 (1H, m), 4.9-4.4 (2H, m), 3.8-2.4 (5H, m), 2.2-1.2 (19H, m).

Ex.166 ($CDCl_3$) δ 7.5 (1H, m), 7.4-7.1 (7H, m), 5.4 and 5.1 (1H, 2xbr,s), 4.5 (2H, m), 4.4 (2H, m), 4.2 (2H, m), 3.75 and 3.72 (3H, 2xs), 3.5 (2H, m), 2.8 (1H, m), 2.5 (1H, m), 1.9 (3H, br, s), 1.6 (6H, m), 1.2 (6H, m).

Ex.167 (d^6-DMSO) δ 12.8 (1H, br s), 7.5 (1H, d), 7.4-6.9 (9H, m), 4.4 (2H, s), 4.1 (1H, m), 3.8 (2H, m), 3.4 and 3.0 (2H, 2xdd), 3.1 and 2.8 (2H, 2xdd), 2.5 (2H, m), 2.45 and 2.0 (2H, 2xdd), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.168 (d^6-DMSO) δ 12.8 (1H, br s), 7.7 (1H, d), 7.4-6.9 (8H, m), 6.8 (1H, t), 4.4 (2H, s), 4.1 (1H, m), 3.9 (2H, m), 3.5 and 3.1 (2H, 2xdd), 2.9 (2H, 2xdd), 2.6 (2H, m), 2.4 and 1.9 (2H, 2xdd), 1.85 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.169 (d^6-DMSO) δ 7.5 (1H, d), 7.4-6.9 (9H, m), 4.4 (2H, s), 4.2-3.8 (3H, m), 3.6 (3H, s), 3.5-2.9 (4H, m), 2.8 (1H, d), 2.5 (2H, m), 2.0 (1H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.170 (d^6-DMSO) δ 7.6 (1H, d), 7.4-6.9 (8H, m), 6.8 (1H, t), 4.4 (2H, s), 4.0 (3H, m), 3.6 (3H, s), 3.6-1.95 (8H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.171 (d^6-DMSO) δ 8.1 (1H, m), 7.9 and 7.5 (1H, 2xm), 7.4-6.9 (14H, m), 4.6-4.2 (3H, m), 3.8-2.4 (8H, m), 1.9 (3H, br,s), 1.6 (6H, m), 1.3 (6H, m).

Ex.172 (d^6-DMSO) δ 8.0-6.8 (16H, m), 4.5-4.0 (4H, m), 3.4-2.4 (6H, m), 1.8 (3H, s), 1.6 (6H, m), 1.2 (6H, m), 1.1 (3H, d).

Ex.173 (d^6-DMSO) δ 8.0-6.9 (16H, m), 4.5-4.0 (3H, m), 3.3-2.5 (8H, m), 1.8 (3H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.174 (d^6-DMSO) δ 10.85 and 10.8 (1H, 2xs), 8.1 (1H, m), 7.7-6.7 (15H, m), 4.5-4.1 (3H, m), 3.8-2.3 (8H, m), 1.9 (3H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.175 ($CDCl_3$) δ 7.6-7.0 (8H, m), 4.8 (2H, m), 4.6 (2H, m), 4.3 (1H, m), 3.6-2.2 (9H, m), 2.1-1.4 (13H, m), 1.2 (6H, s).

Ex.176 ($CDCl_3$) δ 7.6-6.7 (8H, m), 4.8-4.0 (5H, m), 3.3-2.0 (9H, m), 1.8-0.8 (19H, m).

Ex.177 ($CDCl_3$) δ 7.1 (1H, m), 7.0-6.6 (8H, m), 5.6 (1H, br,s), 4.3 (1H, s), 4.1 (1H, s), 3.3 (1H, m), 2.9 (1H, d), 2.7 (1H, d), 0.9 (16H, m), 0.6 (6H, t).

Ex.178 (d^6-DMSO) δ 12.8 (1H, br s), 7.7 (1H, m), 7.4-6.9 (8H, m), 6.7 and 6.6 (1H, 2xm), 4.4 (2H, m), 4.3-3.8 (3H, m), 3.4-2.8 (4H, m), 2.5 (2H, m), 2.1 (1H, m), 1.9 (3H, s), 1.6 (7H, m), 1.3 (6H, m).

Ex.179 (d^6-DMSO) δ 12.8 (1H, br s), 7.7 (1H, m), 7.5-7.0 (8H, m), 6.7 and 6.6 (1H, 2xm), 4.4 (2H, m), 4.3-3.5 (3H, m), 3.4-2.9 (4H, m), 2.5 (2H, m), 2.1 (1H, m), 1.9 (3H, s), 1.6 (7H, m), 1.3 (6H, m).

Ex.180 (d^6-DMSO) δ 8.3-6.9 (10H, m), 4.5 (2H, m), 4.0-2.5 (8H, m), 1.9 (4H, m), 1.7 (9H, m), 1.4-1.2 (9H, m).

Ex.181 (d^6-DMSO) δ 8.3 and 8.25 (1H, 2t), 7.7-6.9 (10H, m), 6.6 and 6.5 (1H, 2s), 4.5 (2H, m), 4.1 and 3.8 (1H, 2m), 3.6-2.4 (8H, m), 2.0-1.5 (13H, m), 1.4 and 1.3 (6H, m).

Ex.182 (d^6-DMSO) δ 8.1-6.8 (18H, m), 4.5-4.1 (3H, m), 3.6-2.4 (8H, m), 1.9 (3H, sm), 1.6 (6H, m), 1.3 (6H, m).

Ex.183 (d^6-DMSO) δ 12.0 (1H, br s), 7.9 (1H, m), 7.4 (4H, m), 7.1-6.8 (5H, m), 4.6-4.3 (3H, m), 3.9 (1H, m), 3.7 (2H, m), 3.5-2.9 (5H, m), 2.6 (2H, m), 1.9-1.5 (11H, m), 1.3 (6H, m).

Ex.184b (d^6-DMSO) δ 12.6 (1H, br s), 8.1 and 6.3 (1H, 2xt), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.2-3.9 (2H, m), 3.5-2.8 (6H, m), 2.6 (2H, m), 2.1-1.5 (13H, m), 1.4-1.1 (9H, m).

Ex.185 (d^6-DMSO) δ 12.6 (1H, br s), 8.0 and 6.3 (1H, 2xm), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.2-3.9 (2H, m), 3.5-2.8 (6H, m), 2.6 (2H, m), 2.1-1.5 (13H, m), 1.4-1.1 (9H, m).

Ex.186b (d^6-DMSO) δ 12.5 (1H, br s), 8.2 and 8.0 (1H, 2xd), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.1 (2H, m), 3.5-2.3 (8H, m), 2.2-1.5

(13H, m), 1.4-1.1 (9H, m).

Ex.187 (d^6-DMSO) δ 12.4 (1H, br s), 8.1 (1H, d), 7.3 (3H, m), 7.1 (5H, m), 4.5 (2H, d), 4.1 (1H, m), 3.9 (1H, m), 3.3-2.9 (6H, m), 2.5 (2H, m), 2.1-1.4 (13H, m), 1.2 (9H, m).

Ex.188 ($CDCl_3$) δ 9.1 and 6.0 (1H, 2xt), 7.6-7.0 (8H, m), 4.6-4.3 (3H, m), 4.1 (1H, m), 3.8 and 3.3 (3H, 2xs), 3.6-3.1 (6H, m), 2.9 (1H, m), 2.7-2.2 (2H, m), 2.0-1.6 (12H, m), 1.4 and 1.2 (6H, 2xs).

Ex.189 ($CDCl_3$) δ 7.6-7.0 (8H, m), 5.9 (1H, m), 4.5 (3H, m), 4.1 (1H, m), 3.7 (3H, s), 3.6-3.4 (4H, m), 3.3 (2H, s), 2.8 (1H, m), 2.6 (1H, m), 2.3 (1H, m), 2.0-1.6 (12H, m), 1.4 (6H, s).

Ex.190 (d^6-DMSO) δ 7.4-6.9 (8H, m), 6.8 (1H, t), 4.8-4.1 (3H, m), 3.6-2.6 (9H, m), 2.5 (2H, m), 1.9-1.4 (13H, m), 1.2 (6H, m).

Ex.191 (d^6-DMSO) δ 7.8 (1H, t), 7.5-6.9 (8H, m), 6.8 and 6.7 (1H, 2xt), 4.8-3.8 (5H, m), 3.6 (3H, m), 3.4-2.9 (4H, m), 2.5 (2H, m), 2.1 (1H, m), 1.9 (3H, br s), 1.7-1.2 (13H, m).

Ex.192 ($CDCl_3$) δ 7.6-7.1 (8H, m), 5.1 and 4.7 (1H 2xm), 4.5 and 4.3 (1H, 2xd), 3.5 (2H, m), 3.4-2.8 (4H, m), 2.4-1.1 (25H, m).

Ex.193 ($CDCl_3$) δ 7.5 (1H, d), 7.4-7.1 (7H, m), 4.6 (1H, m), 4.2 (1H, m), 3.5 (2H, m), 3.2 (2H, m), 2.9 (1H, m), 2.3 (1H, m), 2.2-1.8 (13H, m), 1.6 (6H, m), 1.2 (6H, m).

Ex.194 (d^6-DMSO) δ 12.5 (1H, br s), 8.1 (1H, t), 7.3 (3H, m), 7.0 (5H, m), 6.3 (1H, t), 4.5 (2H, m), 3.9 (1H, m), 3.7 (2H, m), 3.4-2.9 (4H, m), 2.7-2.3 (4H, m), 2.1 (1H, m), 1.8 (3H, s), 1.6 (9H, m), 1.3 (6H, s).

Ex.195 ($CDCl_3$) δ 7.7-7.1 (8H, m), 6.9 and 6.0 (1H 2xt), 4.6(3H, m), 4.4-4.0 (3H, m), 3.8 (1H, m), 3.5 (4H, m), 3.2 (2H, m), 2.8 (1H, m), 2.3 (2H, m), 1.9 (6H, m), 1.8-1.2 (22H, m).

Ex.196 ($CDCl_3$) δ 7.6 (1H, d), 7.5-7.1 (7H, m), 6.9 (1H, d), 5.8

and 5.2 (2H, dd), 4.5(3H, m), 4.3 (1H, m), 3.5 (4H, m), 3.2 (1H, d), 2.9 (1H, m), 2.5-2.1 (2H, m), 2.0-1.1 (30H, m).

Ex.197 (d^6-DMSO) δ 8.2 and 6.7 (1H,2xm), 7.4-6.8 (10H, m), 4.5 (2H, m), 4.1 and 3.8 (1H, 2xm), 3.6-2.5 (6H, m), 1.9 (3H, m), 1.8-1.5 (10H, m), 1.4 and 1.2 (6H, 2xs).

Ex.198b (d^6-DMSO) δ 12.6 (1H, br s), 8.0 (1H, t), 7.4 (3H, m), 7.0 (6H, m), 4.5 (2H, d), 4.1 (1H, m), 3.6 (2H, m), 3.4-2.8 (4H, m), 2.6-2.2 (4H, m), 1.9 (3H, s), 1.6 (10H, m), 1.35 (6H, s).

Ex.199 (d^6-DMSO) δ 12.6 (1H, br s), 8.1 (1H, t), 7.3 (3H, m), 7.0 (5H, m), 6.4 (1H, t), 4.5 (2H, m), 3.9 (1H, m), 3.6 (2H, m), 3.4-2.9 (4H, m), 2.6-2.4 (4H, m), 2.1 (1H, m), 1.8 (3H, s), 1.6 (9H, m), 1.2 (6H, s).

Ex.200 (d^6-DMSO) δ 12.6 (1H, br s), 8.0 (1H, d), 7.3 (3H, m), 7.0 (6H, m), 4.5 (2H, m), 4.0 (2H, m), 3.4-2.8 (4H, m), 2.6-2.1 (5H, m), 1.9 (3H, s), 1.6 (9H, m), 1.2 (9H, m).

Ex.201 (d^6-DMSO) δ 12.6 (1H, br s), 8.0 (1H, d), 7.3 (3H, m), 7.0 (5H, m), 6.3 (1H, t), 4.5 (2H, d), 4.1 (1H, m), 3.9 (1H, m), 3.4-2.9 (4H, m), 2.6-2.4 (4H, m), 2.0 (1H, m), 1.9 (3H, s), 1.6 (9H, m), 1.2 (9H, m).

Ex.202 (d^6-DMSO) δ 12.6 (1H, br s), 8.0 (1H, d), 7.3 (3H, m), 7.0 (6H, m), 4.5 (2H, d), 4.1 (2H, m), 3.5-2.8 (4H, m), 2.7-2.2 (5H, m), 1.9 (3H, s), 1.6 (9H, m), 1.4-1.1 (9H, m).

Ex.203 (d^6-DMSO) δ 12.6 (1H, br s), 8.1 (1H, d), 7.3 (3H, m), 7.0 (5H, m), 6.4 (1H, t), 4.5 (2H, d), 4.1 (1H, m), 3.9 (1H, m), 3.4-2.9 (4H, m), 2.7-2.3 (4H, m), 2.0 (1H, m), 1.8 (3H, s), 1.6 (9H, m), 1.2 (9H, m).

Ex.204 ($CDCl_3$) δ 7.6-7.1 (8H, m), 5.1-4.5 (3H, m), 4.0 (1H, m), 3.6-2.2 (10H, m), 2.0-1.4 (13H, m), 1.2 (6H, m).

Ex.205 ($CDCl_3$) δ 7.6 (1H, m), 7.4-7.0 (7H, m), 6.8 (1H, m), 5.8

(1H, dd), 4.7-4.4 (4H, m), 3.8 and 3.75 (3H, 2xs), 3.6-2.2 (6H, m), 2.0-1.4 (13H, m), 1.2 (6H, m).

Ex.206 ($CDCl_3$) δ 7.7-7.1 (8H, m), 4.5 (3H, m), 3.9 (1H, m), 3.7 and 3.6 (3H, 2xs), 3.5-2.1 (10H, m), 2.0-1.5 (13H, m), 1.2 (6H, m).

Ex.207 (d^6-DMSO) δ 8.0 (1H, t), 7.5 (1H, d), 7.4-6.8 (16H, m), 4.4 (2H, s), 4.1 (1H, m), 3.6-3.1 (3H, m), 2.9 (3H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, s).

Ex.208 (d^6-DMSO) δ 8.0 (1H, t), 7.8 (1H, d), 7.5 (1H, t), 7.4-6.9 (15H, m), 4.5 (1H, s), 4.3 (1H, m), 4.2 (1H, s), 3.6-3.0 (4H, m), 2.7 (2H, m), 2.5 (2H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.209 ($CDCl_3$) δ 7.4-7.0 (8H, m), 5.6 (1H, t), 4.6 (1H, s), 4.4 (1H, s), 2.9 (3H, m), 2.3 (2H, dd), 2.0 (3H, s), 1.6 (6H, m), 1.3 (1H, d), 1.2 (6H, s).

Ex.210 ($CDCl_3$) δ 7.2 (8H, m), 7.1 and 6.2 (1H, 2xd), 5.7 and 5.6 (1H, 2xt), 4.7-4.2 (3H, m), 3.7 (3H, s), 3.0-2.2 (5H, m), 2.0 (3H, s), 1.7 (7H, m), 1.43 and 1.40 (6H, 2xs), 1.3 and 1.1 (3H, 2xd).

Ex.211 ($CDCl_3$) δ 7.5-7.0 (8H, m), 5.8 and 5.6 (1H, 2xt), 4.8-4.3 (3H, m), 3.9-3.2 (3H, m), 3.0 (3H, m), 2.6-1.0 (21H, m).

Ex.212 ($CDCl_3$) δ 7.5 (1H, d), 7.4-7.1 (7H, m), 6.2 (1H, d), 5.8 (1H, t), 4.5 (2H, d), 3.8 (1H, m), 3.2 (2H, dd), 2.8 (1H, m), 2.7 (1H, m), 2.4 (1H, m), 2.0 (3H, s), 1.8-1.1 (18H, m).

Ex.213 ($CDCl_3$) δ 7.5-7.1 (8H, m), 6.3 (1H, d), 5.7 (1H, t), 4.5 (2H, d), 3.8 (1H, m), 3.2 (2H, dd), 2.8 (1H, m), 2.7 (1H, m), 2.5 (1H, m), 2.0 (3H, s), 1.8-1.1 (18H, m).

Ex.214 ($CDCl_3$) δ 7.6-6.8 (9H, m), 6.0 (1H, m), 4.8-4.2 (4H, m), 3.8 (3H, s), 3.6-2.1 (7H, m), 2.0-1.1 (21H, m).

Ex.215 ($CDCl_3$) δ 7.6-7.1 (8H, m), 5.1-4.5 (3H, m), 4.0 (1H, m), 3.6-2.2 (10H, m), 2.0-1.4 (13H, m), 1.2 (6H, m).

Ex.216 (d^6-DMSO) δ 8.0-7.0 (15H, m), 6.8-6.5 (2H, m), 4.5-4.0 (3H, m), 3.4-3.0 (4H, m), 2.5 (2H, m), 1.82 and 1.78 (3H, 2xs), 1.6 (6H, m), 1.1 and 1.2 (6H, 2xs).

Ex.217 (d^6-DMSO) δ 8.2-6.8 (16H, m), 6.5 (1H, t), 4.5-4.1 (3H, m), 3.4-2.2 (6H, m), 1.8 and 1.7 (3H, 2xs), 1.6 (6H, m), 1.1 and 1.2 (6H, 2xs).

Ex.218 (d^6-DMSO) δ 8.0 (1H, t), 7.7 (1H, d), 7.4-6.7 (14H, m), 4.5-4.0 (4H, m), 3.6-2.3 (6H, m), 1.8 (3H, s), 1.6 (6H, m), 1.3-1.0 (9H, m).

Ex.219 (d^6-DMSO) δ 12.6 (1H, br s), 7.4-6.9 (13H, m), 5.0-4.0 (4H, m), 3.6-3.0 (3H, m), 2.8-2.1 (4H, m), 1.7 (3H, br s), 1.6 (6H, m), 1.1 and 1.08 (6H, 2xs).

Ex.220c ($CDCl_3$) δ 7.6-7.0 (8H, m), 4.8-4.3 (3H, m), 3.8-2.3 (9H, m), 2.2-1.4 (19H, m).

Ex.221 ($CDCl_3$) δ 7.6-7.0 (8H, m), 6.4 (1H, m), 4.6-4.4 (2H, m), 4.3-4.0 (1H, m), 3.9-3.1 (9H, m), 2.9-2.6 (2H, m), 2.3 (1H, m), 2.1-1.9 (6H, m), 1.6 (6H, m), 1.4 and 1.2 (6H, 2 x s).

Ex.222 ($CDCl_3$) δ 7.6-6.9 (8H, m), 5.5 (1H, m), 4.5 (2H, m), 4.2 (1H, m), 3.7-3.1 (8H, m), 2.9 (1H, m), 2.7 (1H, m), 2.2-1.7 (7H, m), 1.5 (9H, m), 1.2 (6H, m).

Ex.223 ($CDCl_3$) δ 7.6-7.0 (8H, m), 6.1 (1H, m), 4.7-4.2 (3H, m), 3.6-3.1 (8H, m), 2.9 (1H, m), 2.3 (1H, m), 2.2-1.8 (7H, m), 1.6 (9H, m), 1.2 (6H, m).

Ex.224b (d^6-DMSO) δ 12.6 (1H, br s), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.2-3.9 (2H, m), 3.5-2.8 (9H, m), 2.6 (2H, m), 2.1-1.5 (13H, m), 1.4-1.1 (9H, m).

Ex.225 (d^6-DMSO) δ 12.6 (1H, br s), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.2-3.9 (2H, m), 3.5-2.8 (9H, m), 2.6 (2H, m), 2.1-1.5 (13H, m), 1.4-1.1 (9H, m).

Ex.226b (d^6-DMSO) δ 12.6 (1H, br s), 8.0 (1H, d), 7.3 (3H, m), 7.0 (5H, m), 4.5 (2H, d), 4.1 (1H, m), 3.9 (1H, m), 3.4-2.9 (7H, m), 2.6-2.4 (4H, m), 2.0 (1H, m), 1.9 (3H, s), 1.6 (9H, m), 1.2 (9H, m).

Ex.227 ($CDCl_3$) δ 7.6-7.0 (9H, m), 6.0 (1H, m), 4.6-4.0 (5H, m), 3.8-3.2 (6H, m), 2.9-2.2 (3H, m), 2.0-1.2 (19H, m).

Ex.228 ($CDCl_3$) δ 7.8-7.1 (9H, m), 6.6 (1H, m), 4.6-4.2 (4H, m), 3.6-3.0 (4H, m), 2.9-2.0 (3H, m), 2.0-1.2 (21H, m).

Ex.229 ($CDCl_3$) δ 8.1 (1H, t), 7.6 (1H, d), 7.4-7.1 (7H, m), 6.0 (1H, t), 4.8 (1H, m), 4.6 (1H, s), 4.4 (1H, s), 4.1 (1H, dd), 3.8 (1H, dd), 3.5 (2H, m), 2.9-2.2 (6H, m), 2.0 (3H, s), 1.6 (6H, m), 1.4 (6H, s).

Ex.230 ($CDCl_3$) δ 7.6-6.9 (9H, m), 5.8 (1H, m), 4.5 (2H, m), 4.2-3.6 (3H, m), 3.2 (2H, m), 2.5 (2H, m), 2.2-1.2 (19H, m).

Ex.231 (d^6-DMSO) δ 12.6 (1H, br s), 8.1 (1H, d), 7.3 (3H, m), 7.0 (5H, m), 4.5 (2H, d), 4.1 (1H, m), 3.9 (1H, m), 3.4-2.9 (7H, m), 2.7-2.3 (4H, m), 2.0 (1H, m), 1.8 (3H, s), 1.6 (9H, m), 1.2 (9H, m).

Ex.232 (d^6-DMSO) δ 12.5 (1H, br s), 8.2 and 8.0 (1H, 2xd), 7.4-6.9 (9H, m), 4.5 (2H, m), 4.1 (2H, m), 3.7 (3H, s), 3.5-2.3 (8H, m), 2.2-1.5 (13H, m), 1.4-1.1 (9H, m).

Ex.233 (d^6-DMSO) δ 12.6 (1H, br s), 8.6 and 8.4 (1H, 2xt), 8.2 and 7.8 (1H, 2xt), 7.6 (1H,m), 7.3 (3H, m), 7.0 (4H, m), 5.0 and 4.7 (1H, 2xd), 4.55 (2H, d), 4.5-4.1 (2H, m), 3.9-3.5 (4H, m), 3.3-2.4 (4H, m), 1.9 (3H, s), 1.6 (6H, m), 1.3 (6H, m).

Ex.234 (d^6-DMSO) δ 12.6 (1H, br s), 8.9 and 8.3 (1H, 2xm), 7.6

(1H, t), 7.3 (3H, m), 7.0 (5H, m), 5.1 and 4.6 (1H, 2xm), 4.5 (1H, s), 4.4 (1H, s), 4.3-3.6 (6H, m), 3.4-2.2 (4H, m), 1.9 (3H, s), 1.6-1.3 (12H, m).

Ex.235 (d^6-DMSO) δ 12.7 (1H, br s), 9.0 (1H, m), 8.6-8.2 (3H, m), 7.7-6.9 (6H, m), 4.9-3.0 (9H, m), 2.8-2.2 (4H, m), 1.9 (3H, m), 1.6-1.3 (12H, m).

Ex.236 (d^6-DMSO) δ 9.4 (1H, s), 8.4 (2H, s), 8.3 (1H, t), 8.1 (1H, s), 7.3 (3H, m), 7.1 (3H, m), 6.9 (2H, m), 4.6 (2H, s), 4.3 (1H, m), 3.5 (2H, m), 3.1 and 3.0 (2H, 2xd), 2.8 and 2.6 (2H, m), 2.1-1.2 (19H, m).

Ex.237 (d^6-DMSO) δ 11.7 (1H, s), 10.2 (1H, s), 8.44 (2H, s), 8.4 (1H, t), 8.1 (1H, s), 7.3 (3H, m), 7.1 (3H, m), 6.9 (2H, m), 4.5 (2H, s), 4.0 (1H, m), 3.5 (2H, m), 3.1 and 3.0 (2H, 2xd), 2.8-2.5 (2H, m), 2.0-1.1 (19H, m).

Ex.238 (d^6-DMSO) δ 8.1 and 8.0 (1H, 2xd) , 7.3 (3H, m), 7.0 (5H, m), 7.0 and 6.3 (1H, 2xt), 4.5 (2H, m), 4.2-2.1 (12H, m), 2.0-1.1 (22H, m).

The compounds of the examples were tested for binding at the CCK_B receptor in mouse cortical membranes by means of a radioligand binding assay. The procedure was as follows:

The whole brains from male mice (CD1 22-25g; Charles River) were removed and placed in ice-cold buffer (pH7.2 @ 21 ± 3°C) of the following composition (mM); 10 HEPES, 130 NaCl, 4.7 KCl, 5 $MgCl_2$, 1 EDTA and containing 0.25g.l^{-1} bacitracin. The cortex was dissected, weighed and homogenised in 40ml ice-cold buffer using a Teflon-in-glass homogeniser. The homogenate was centrifuged at 39,800g for 20 min at 4°C, the supernatant discarded and the pellet resuspended by homogenisation in fresh buffer. The homogenate was recentrifuged (39,800g; 20 min @ 4°C) and the final pellet was resuspended in HEPES buffer to give a tissue concentration of 2mg.ml^{-1} (original wet weight).

The membranes (400ml) were incubated for 150 min at 21 ± 3°C in a final volume of 0.5ml with HEPES buffer containing [^{125}I]-CCK8S (0.05ml; 200pM NEN 2200Ci.mmol^{-1}) and competing compound. Total and non-specific binding of [^{125}I]-CCK8S were defined using 0.05ml of buffer and 0.05ml of 10mM L-365,260, respectively. The assay was terminated by rapid filtration through pre-soaked Whatman GF/B filters using a Brandell Cell harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH7.4 @ 4°C) and bound radioactivity determined by counting (1 min.) in a gamma-counter.

The results obtained from the CCK_B assays are set out in Table 1.

TABLE 1

Example	CCK_B pK_i	Example	CCK_B pK_i
1	5.0	32	5.5
2	5.1	33	6.0
3	4.8	34	6.6
4	5.6	35	5.1
5	5.3	36	6.1
6	5.3	37	6.6
7	4.8	38	6.0
8	5.2	39	5.8
9	5.0	40	6.0
10	4.8	42	6.8
11	5.0	43	6.2
12	6.2	44	5.3
13	6.0	45	5.2
14	6.3	46	6.1
15	5.8	47	6.3
16	5.7	48	6.0
17	5.7	49	5.9
19	4.5	50	6.6
20	5.5	51	7.2
21	5.2	52	6.6
23	5.5	53	6.5
24	5.9	54	6.1
25	6.7	55	6.1
26	5.5	56	6.6
27	6.9	57	6.7
28	5.9	58	6.6
29	5.9	59	5.6
30	5.7	60	6.4
31	5.5	61	5.9

TABLE 1 (continued)

Example	CCK_B pK_i	Example	CCK_B pK_i
62	5.6	93	5.3
63	5.9	94	5.2
64	5.3	95	5.5
65	6.5	96	6.7
66	6.2	97	5.9
67	5.6	98	6.7
68	5.9	99	5.5
69	6.2	100	6.2
70	5.0	101	5.6
71	5.8	102	5.6
72	5.8	103	5.2
73	5.3	104	4.9
74	7.3	105	6.2
75	5.9	106	4.5
76	5.7	107	4.2
77	6.5	108	4.7
78	6.2	110	4.9
79	5.5	111	7.0
80	5.8	112	5.7
81	7.3	113	5.6
82	5.1	114	5.3
83	5.1	115	6.0
84	5.2	116	5.7
85	5.8	117	5.3
86	6.2	118	6.1
87	5.3	119	6.7
88	5.3	120	7.0
89	6.1	121	4.8
92	5.6	122	6.2

TABLE 1 (continued)

Example	CCK_B pK_i	Example	CCK_B pK_i
123	5.8	153	6.2
124	5.8	154	6.5
125	5.5	155	6.5
126	5.4	156	7.3
127	5.3	157	6.7
128	5.8	158	5.7
129	6.5	159	4.6
130	6.3	160	6.4
131	7.4	161	6.2
132	6.5	162	5.6
133	6.1	163	5.0
134	5.9	164	6.3
135	6.3	165	6.0
136	6.3	166	6.0
137	5.8	167	5.0
138	4.6	168	5.1
139	5.3	169	5.1
140	5.0	170	5.4
141	5.8	171	6.7
142	5.9	172	5.8
143	7.2	173	6.1
144	6.2	174	6.1
145	6.2	175	6.1
147	6.3	176	5.2
148	5.2	177	5.5
149	6.1	178	5.3
150	5.4	179	5.2
151	6.6	180	6.3
152	6.0	181	5.5

TABLE 1 (continued)

Example	CCK_B pK_i	Example	CCK_B pK_i
182	5.5	206	6.9
183	6.3	207	5.5
184	6.2	208	6.2
185	6.8	209	6.5
186	7.1	210	5.2
187	6.2	211	5.8
188	6.2	212	6.1
189	5.7	213	5.8
190	5.8	214	5.7
191	5.2	215	6.1
192	5.3	216	6.3
193	5.5	217	6.3
194	5.8	218	6.4
195	6.1	219	6.2
196	6.2	220	7.0
197	4.5	227	5.0
198	5.1	228	5.4
199	6.1	229	5.5
200	5.0	230	5.3
201	6.5	233	6.5
202	5.2	234	6.5
203	5.9	236	6.7
204	6.0	237	6.7
205	6.7	238	7.6

The compounds of the examples were also tested for gastrin antagonist activity in an immature rat stomach assay. The procedure was as follows:

The oesophagus of immature rats (33-50 g, ca. 21 days old) was

ligated at the level of the cardiac sphincter and the duodenal sphincter was cannulated. The stomach was excised and flushed with ca. 1 ml of unbuffered physiological saline solution. The fundus was punctured and cannulated. A further 4-5 ml of unbuffered solution was flushed through the stomach to ensure the preparation was not leaking. The stomach was lowered into a jacketed organ bath containing 40 ml of buffered solution containing $3x10^{-8}$M 5-methylfurmethide, maintained at 37° and gassed vigorously with 95% O_2/ 5% CO_2. The stomach was continuously perfused at a rate of 1 ml min^{-1} with unbuffered solution gassed with 100% O_2 with the perfusate passing over an internally referenced pH-electrode fixed 12 cm above the stomach.

After 120 min of stabilisation the drugs were added directly to the serosal solution in the organ bath and after a further 60 min cumulative pentagastrin dose-response curves were started. Changes in acid secretion were monitored and the curves analysed according to Black et.al., Br. J. Pharmacol., 1985, 86, 581.

The results obtained from the gastrin assays are set out in Table 2.

TABLE 2

Example	Gastrin pK_B	Example	Gastrin pK_B
12	4.8	70	5.7
13	5.8	71	5.7
14	5.9	73	5.8
15	5.7	78	6.9
16	5.6	79	5.6
22	5.2	81	5.9
23	5.2	83	5.4
24	5.7	84	5.6
25	6.7	85	6.2
27	6.5	90	4.6
28	6.0	91	4.6
29	5.8	94	4.9
35	5.7	99	5.6
36	5.5	103	5.9
39	4.7	109	5.6
41	5.5	112	6.2
48	6.6	113	4.9
49	5.8	119	6.9
50	6.1	120	6.9
51	5.6	122	6.7
56	5.2	123	7.2
62	5.3	124	6.5
64	5.2	129	6.7
65	5.4	131	6.0
67	5.1	132	5.7
68	6.5	133	6.9
69	7.1	136	6.0

TABLE 2 (continued)

Example	Gastrin pK_B	Example	Gastrin pK_B
142	6.1	188	7.3
143	6.9	189	6.9
144	5.6	195	6.9
145	6.3	196	7.0
147	6.9	198	5.2
149	6.2	199	6.3
151	5.9	201	7.0
156	5.7	203	6.4
158	6.4	204	6.1
160	7.0	205	6.2
161	6.6	206	6.0
162	6.1	209	5.7
164	6.6	210	5.1
165	5.9	211	6.0
166	5.7	213	6.1
167	5.5	214	6.6
171	6.5	215	5.5
172	5.4	220	7.3
173	5.8	227	6.2
180	6.2	228	5.8
181	5.7	229	6.4
183	6.5	230	5.8
184	6.6	233	6.4
185	7.1	234	5.5
186	7.3	236	6.9
187	6.9	237	6.8

The compounds of the examples were also tested in a CCK_A binding assay as follows:

The pancreatata were removed from male guinea-pigs (200-300g; Dunkin Hartley) and placed in ice-cold HEPES buffer (pH 7.2 @ 21 ± 3°). The pancreatata were homogenised in 40 ml ice-cold HEPES buffer using a polytron (Brinkmann, PT10, setting 10). 4 x 1 second.

The homogenate was centrifuged at 39,800g for 15 min at 4°. The supernatant was discarded and the pellet re-suspended using a Teflon-in-glass homogeniser in 20 volumes of fresh buffer and re-centrifuged as above. The final pellet was re-suspended using a Teflon-in-glass homogeniser to a tissue concentration of 1 $mg.ml^{-1}$ (original wet weight), and filtered through 500 µm pore-size Nytex mesh.

The membranes (400µl; containing 0.375 µM PD134,308) are incubated for 150 minutes at 21 ± 3° in a final volume of 0.5ml with HEPES buffer containing [^{125}I]-CCK_8(S) (50µl; 200pM) and competing compound. Total and non-specific binding of [^{125}I]-CCK_8(S) are defined using 50µl of buffer and 50µl of 100nM L-364,718 respectively. The assay is terminated by rapid filtration through pre-soaked Whatman GF/B filters using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris HCl (pH 7.4 at 4°) and bound radioactivity is determined by counting (1 min) in a gamma counter.

The results are set out in Table 3.

TABLE 3

Example	CCK_A pK_i	Example	CCK_A pK_i
3	5.3	52	6.0
6	4.8	53	5.3
7	5.4	54	5.9
8	5.3	55	6.6
9	5.1	57	6.7
11	4.9	58	6.4
12	5.7	60	5.2
13	5.5	61	5.3
14	5.1	62	4.8
15	4.7	63	5.1
22	5.3	64	5.1
24	5.2	65	5.9
27	5.4	66	5.4
28	5.0	67	5.0
30	4.6	69	5.1
32	4.7	70	4.8
33	4.9	71	4.9
34	5.5	73	5.4
35	4.9	74	4.9
36	5.5	75	5.4
37	5.1	76	5.3
38	5.2	77	5.2
39	4.9	78	5.1
40	5.1	79	5.1
41	4.8	80	4.8
42	4.8	81	5.3
44	5.1	82	5.3
45	5.3	83	4.9
48	5.1	84	4.9
49	4.9	85	5.0
51	5.5	86	5.6

TABLE 3 (continued)

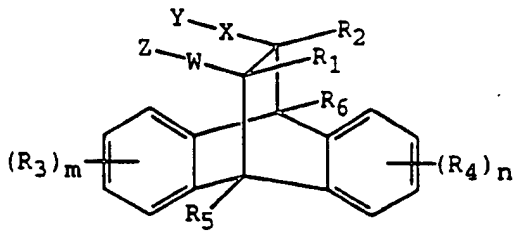
Example	CCK_A pK_i	Example	CCK_A pK_i
87	5.0	122	5.1
88	4.9	123	5.6
89	5.3	124	5.3
90	4.8	125	4.9
91	4.7	126	5.3
92	5.8	127	4.8
93	5.8	128	5.1
94	5.2	129	4.9
95	5.1	130	5.0
96	5.5	131	5.0
97	5.1	132	5.0
98	5.2	133	5.2
99	5.0	134	5.4
100	5.3	135	5.1
101	4.9	137	5.2
102	5.3	138	5.2
103	5.2	139	5.2
104	5.2	140	5.2
105	5.3	141	4.8
107	4.5	142	5.4
108	5.5	143	5.3
111	5.6	144	5.6
112	5.9	145	5.2
113	5.4	146	4.9
114	5.5	147	5.3
115	5.3	148	5.7
117	5.7	149	5.2
118	5.6	150	5.1
119	4.8	151	5.5
120	5.4	152	5.5
121	5.0	153	5.5

TABLE 3 (continued)

Example	CCK_A pK_i	Example	CCK_A pK_i
154	5.5	186	4.6
155	5.2	187	5.2
156	5.3	189	5.9
157	5.7	190	4.9
158	5.1	191	5.1
159	5.7	192	5.0
160	5.1	193	5.2
162	5.6	194	5.1
163	5.9	195	5.9
164	4.4	196	5.9
165	5.3	197	5.7
166	5.2	199	5.9
167	5.0	200	5.5
168	4.8	201	5.1
169	5.7	202	4.9
170	5.2	203	5.2
171	5.8	205	5.3
172	5.6	206	5.7
173	5.4	207	6.6
174	6.2	208	5.7
175	5.3	209	5.3
176	4.7	210	5.1
177	5.8	212	5.1
178	4.9	213	5.1
179	5.0	214	5.5
180	4.4	215	4.5
181	4.9	219	5.6
182	5.3	220	6.3
183	5.1	227	6.3
184	5.1	228	5.4
185	4.9	229	5.5

CLAIMS

1. A compound of the formula



wherein

W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group or $-C(O)-CH_2-$ (in which the carbonyl group is bonded to Y), provided that at least one of W and X contains carbonyl,

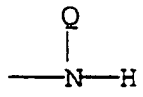
Y is R_7-O- or $R_7-N(R_8)-$ (wherein R_7 is H or C_1 to C_{15} hydrocarbyl, up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom provided that Y does not contain a -O-O- group, and R_8 is H, C_1 to C_3 alkyl, carboxymethyl or esterified carboxymethyl),

Z is selected from

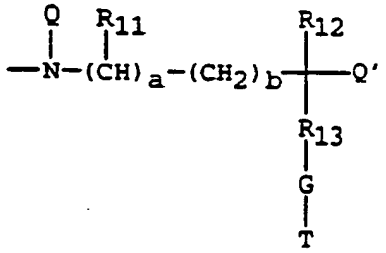
i) $-O-R_9$

wherein R_9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

ii)



wherein Q is H, C_1 to C_5 hydrocarbyl, or $-R_{10}-U$, wherein R_{10} is a bond or C_1 to C_3 alkylene and U is aryl, substituted aryl, heterocyclic, or substituted heterocyclic,

iii) 

wherein a is 0 or 1 and b is from 0 to 3,

R_{11} is H or methyl,

R_{12} is H or methyl; or R_{12} is $CH_2=$ and Q' is absent; or R_{11} and R_{12} are linked to form a 3- to 7-membered ring,

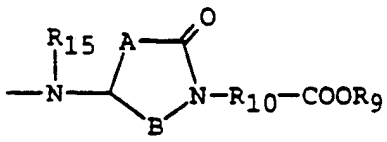
R_{13} is a bond or C_1 to C_5 hydrocarbylene,

G is a bond, -CHOH- or -C(O)-

Q' is as recited above for Q or $-R_{10}-(C(O))_d-L-(C(O))_e-R_9$ (wherein R_9 and R_{10} are as defined above, L is O, S or $-N(R_{14})-$, in which R_{14} is as defined above for R_9, and d and e are 0 or 1, provided that d+e<2); or Q' and R_{12}, together with the carbon atom to which they are attached, form a 3- to 7-membered ring,

Q is as defined above; or Q and R_{12} together form a group of the formula $-(CH_2)_f-V-(CH_2)_g-$ wherein V is -S-, -S(O)-, $-S(O)_2-$, $-CH_2-$, -CHOH- or -C(O)-, f is from 0 to 2 and g is from 0 to 3; or, when Q' is $-R_{10}-U$ and U is an aromatic group, Q may additionally represent a methylene link to U, which link is *ortho* to the R_{10} link to U,

T is H, cyano, C_1 to C_2 alkyl, $-CH_2OH$, carboxy, esterified carboxy or amidated carboxy; or

iv) 

wherein A and B are independently a bond or C_1 to C_3 alkylene, provided that A and B together provide from 2 to 4 carbon atoms in the ring, R_9 and R_{10} are as defined above, and R_{15} is as defined above for R_8

or Z is absent and W is H,

R_1 is H, methyl, halo, carboxy, esterified carboxy, amidated carboxy, carboxymethyl, esterified carboxymethyl or amidated carboxymethyl,

R_2 is selected from the groups recited above for R_1; or, when Z is absent and W is H, R_2 may additionally represent -C(O)-Z' wherein Z' is selected from the groups recited above for Z; or R_1 and R_2 together form a second bond between the carbon atoms to which they are attached,

R_3 and R_4 (or each R_3 and R_4 group, when m or n is 2 or more) are independently selected from halo, amino, nitro, cyano, sulphamoyl, C_1 to C_3 alkyl, C_1 to C_3 alkoxy, carboxy, esterified carboxy and amidated carboxy,

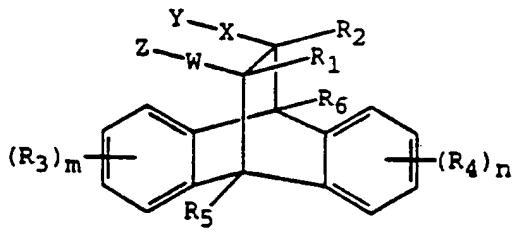
R_5 and R_6 are independently selected from H and the groups recited above for R_3

m is from 0 to 4, provided that m is not more than 2 unless R_3 is exclusively halo,

n is from 0 to 4, provided that n is not more than 2 unless R_4 is exclusively halo,

or a pharmaceutically acceptable salt thereof, for use in therapy.

2. A compound of the formula



wherein

W is a carbonyl, sulphonyl or sulphinyl group, and X is a carbonyl, sulphonyl or sulphinyl group or $-C(O)-CH_2-$ (in which the carbonyl group is bonded to Y), provided that at least one of W and X contains carbonyl,

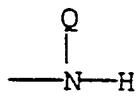
Y is R_7-O- or $R_7-N(R_8)-$ (wherein R_7 is H or C_1 to C_{15} hydrocarbyl, up to two carbon atoms of the hydrocarbyl moiety optionally being replaced by a nitrogen, oxygen or sulphur atom provided that Y does not contain a -O-O- group, and R_8 is H, C_1 to C_4 alkyl, carboxymethyl or esterified carboxymethyl),

Z is selected from

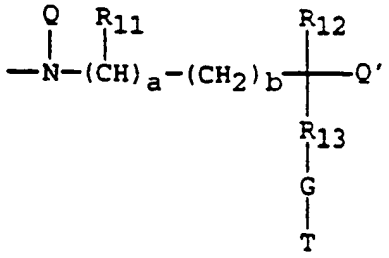
i) $-O-R_9$

wherein R_9 is H, C_1 to C_6 alkyl, phenyl, substituted phenyl, benzyl or substituted benzyl;

ii)



wherein Q is H, C_1 to C_6 hydrocarbyl, or $-R_{10}-U$, wherein R_{10} is a bond or C_1 to C_3 alkylene and U is aryl, substituted aryl, heterocyclic, or substituted heterocyclic,

iii) 

wherein a is 0 or 1 and b is from 0 to 3,

R_{11} is H or methyl,

R_{12} is H or methyl; or R_{12} is CH_2= and Q' is absent; or R_{11} and R_{12} are linked to form a 3- to 7-membered ring,

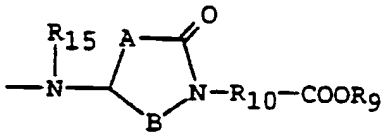
R_{13} is a bond or C_1 to C_6 hydrocarbylene,

G is a bond, -CHOH- or -C(O)-

Q' is as recited above for Q or $-R_{10}-(C(O))_d-L-(C(O))_e-R_9$ (wherein R_9 and R_{10} are as defined above, L is O, S or $-N(R_{14})-$, in which R_{14} is as defined above for R_2, and d and e are 0 or 1, provided that d+e<2); or Q' and R_{12}, together with the carbon atom to which they are attached, form a 3- to 7-membered ring,

Q is as defined above; or Q and R_{12} together form a group of the formula $-(CH_2)_f-V-(CH_2)_g-$ wherein V is -S-, -S(O)-, $-S(O)_2-$, $-CH_2-$, -CHOH- or -C(O)-, f is from 0 to 2 and g is from 0 to 3; or, when Q' is $-R_{10}-U$ and U is an aromatic group, Q may additionally represent a methylene link to U, which link is *ortho* to the R_{10} link to U,

T is H, cyano, C_1 to C_4 alkyl, $-CH_2OH$, carboxy, esterified carboxy or amidated carboxy; or

iv) 

wherein A and B are independently a bond or C_1 to C_3 alkylene, provided that A and B together provide from 2 to 4 carbon atoms in the ring, R_9 and R_{10} are as defined above, and R_{15} is as defined above for R_8

or Z is absent and W is H,

R_1 is H, methyl, halo, carboxy, esterified carboxy, amidated carboxy, carboxymethyl, esterified carboxymethyl or amidated carboxymethyl,

R_2 is selected from the groups recited above for R_1; or, when Z is absent and W is H, R_2 may additionally represent -C(O)-Z' wherein Z' is selected from the groups recited above for Z; or R_1 and R_2 together form a second bond between the carbon atoms to which they are attached,

R_3 and R_4 (or each R_3 and R_4 group, when m or n is 2 or more) are independently selected from halo, amino, nitro, cyano, sulphamoyl, C_1 to C_3 alkyl, C_1 to C_3 alkoxy, carboxy, esterified carboxy and amidated carboxy,

R_5 and R_6 are independently selected from H and the groups recited above for R_3

m is from 0 to 4, provided that m is not more than 2 unless R_3 is exclusively halo,

n is from 0 to 4, provided that n is not more than 2 unless R_4 is exclusively halo,

or a pharmaceutically acceptable salt thereof, provided that

if one (but only one) of R_1 and R_2 is methyl, m and n are not both 0,

Z is not methoxy when Y is methoxy,

Z and Y are not *trans* to each other when Z is R_8-O- and Y is R_7-O- , and

if Z is absent and R_1 and R_2 are both H, Y is not R_7-O-.

3. A compound according to claim 1 or claim 2 wherein R_7 is C_6 to C_8 straight or branched chain alkyl, or R_{25}-$(CH_2)_p$-, wherein R_{25} is selected from phenyl, 1-naphthyl, 2-naphthyl, indolyl, norbornyl, adamantyl or cyclohexyl, and p is from 0 to 3.

4. A compound according to any preceding claim wherein W is carbonyl and X is sulphonyl.

5. A compound according to any of claims 1 to 3 wherein W is carbonyl and X is carbonyl.

6. A compound according to any of claims 1 to 3 wherein W is sulphonyl and X is carbonyl.

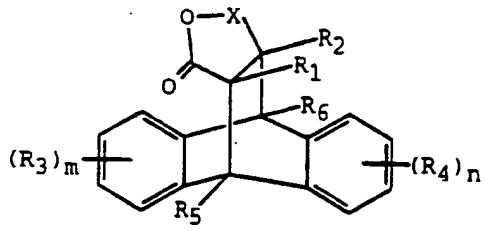
7. A compound according to any preceding claim wherein R_1 and R_2 are both H.

8. A compound according to any preceding claim wherein m and n are both 0.

9. A pharmaceutical composition comprising a compound according to any preceding claim, together with a pharmaceutically acceptable diluent or carrier.

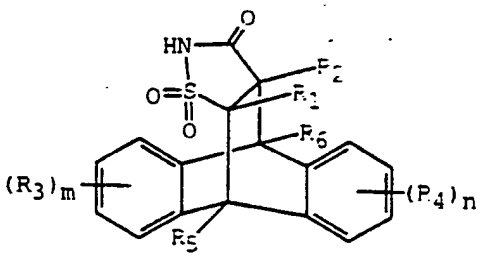
10. A method of making a compound according to claim 2 wherein W is carbonyl, said method including the step of reacting

a compound of the formula



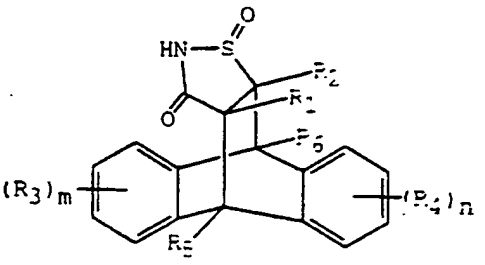
with a compound of formula YH, wherein Y is as defined in claim 2.

11. A method of making a compound according to claim 2 wherein W is sulphonyl, said method comprising the step of reacting a compound of the formula



with a compound of the formula R_7-Hal, wherein Hal represents a halogen atom and R_7 is as defined in claim 2, and then reacting the product with an alkoxide.

12. A method of making a compound according to claim 2 wherein W or X is sulphinyl, said method comprising the step of reacting a compound of the formula:



with a compound of the formula R--Hal, wherein Hal represents a

halogen atom and R_7 is as defined in claim 2, and then reacting the product with an alkoxide.

13. A method of making a pharmaceutical composition according to claim 9, comprising mixing a compound according to any of claims 1 to 8 with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00346

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C233/63; C07C233/58; C07C237/22; C07D207/16
C07D211/60; C07D209/20; C07K5/06; A61K31/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07D ; C07K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	US,A,3 950 407 (HAMMAR) 13 April 1976 see example 2 ---	2,5,7,8
X	JOURNAL OF ORGANIC CHEMISTRY. vol. 53, no. 25, 9 December 1988, EASTON US pages 5831 - 9 E. WEBER ET. AL. 'Design of Roof-Shaped Clathrate Hosts. Inclusion Properties and X-ray Crystal Structures of a Free Host and of Inclusion Compounds with 1-BuOH and DMF' see page 5832, column 1 --- -/--	2,5,7,8

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 MAY 1993	28. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	HELPS I.M.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS vol. 1984, no. 23, December 1984, LETCHWORTH GB pages 1632 - 4 M. CZUGLER ET. AL. 'Selective Clathrate Formation with the New Host System cis-and trans-9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid: Inclusion Properties and X-ray Structure of an Encapsulated Acetic Acid Dimer.' see whole document	2,5,7,8
X	CHEMICAL ABSTRACTS, vol. 101, no. 25, 17 December 1984, Columbus, Ohio, US; abstract no. 229865n, A.K.SINGH ET. AL. 'PMR Spectral Studies of Diels-Alder adducts: Anthracene-crotonic acid, anthracene-fumaric acid and beta-naphthol-fumaric acid' page 712 ;column 1 ; see abstract & INDIAN J. CHEM., SECT.B, vol. 23B, 1984, pages 631 - 4	2,3,5,7,8
X	CHEMICAL ABSTRACTS, vol. 73, no. 1, 6 July 1970, Columbus, Ohio, US; abstract no. 3689z, I. NANU ET. AL. 'Esters of 9,10-dihydroanthracene-endo-alpha-beta-succinic acid as models for the study of large molecule plasticisers' page 314 ;column 2 ; see abstract & BUL. STIINT. TEH. INST. POLITEH. TIMISOARA vol. 14, no. 1, 1969, pages 141 - 6 & 8TH COLLECTIVE INDEX page 11654S see page 11654S, column 1, line 6 - line 59	2,3,5,7,8
A	EP,A,0 405 537 (WARNER LAMBERT) 2 January 1991 see claims; examples	1-13
A	US,A,3 577 366 (KLANDERMAN ET. AL.) 4 May 1971 see claims; examples 8,9	1-8

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	US,A,4 306 063 (UMEN) 15 December 1981 see column 2, line 9 - line 24; claims; example 2 ---	1-13
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 94, no. 5, 8 March 1972, GASTON, PA US pages 1693 - 8 G.A. RUSSELL ET. AL. 'Aliphatic Semidiones. XIX. Polycyclic Derivatives of Cyclobutanesemidione' see page 1698, column 2, paragraph 2 -paragraph 5 -----	1-8

INTERNATIONAL SEARCH REPORT

ernational application No.

PCT/GB93/00346

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The formulation of the claims is so complex that a complete search is not possible within a reasonable time limit. Also, vague definitions such as "substituted phenyl", "substituted heterocycle", "esterified carboxy" are used. Search carried out on the basis of synthesised examples (See Guidelines B-III,3.7)

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300346
SA 70530

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 17/05/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-3950407	13-04-76	US-A- 4104475	01-08-78
		US-A- 4209633	24-06-80
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		CN-A- 1049165	13-02-91
		EP-A- 0479910	15-04-92
		JP-T- 4506079	22-10-92
		WO-A- 9100274	10-01-91
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		US-A- 3457235	22-07-69
		US-A- 3720701	13-03-73
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